PCT/KR2004/000097

1

JC17 Rec'd PUI/AID 22 JUL 2005

## GLYCOGEN SYNTHASE KINASE 3BETA INHIBITOR, COMPOSITION AND PROCESS FOR THE PREPARATION THEROF

#### Field of the Invention

5

The present invention relates to a compound for inhibiting glycogen synthase kinase 3beta (GSK-3 $\beta$ ) activity, a pharmaceutical composition containing the compound as an active ingredient and a process for the preparation thereof.

10

15

20

25

30

35

#### Background of the Invention

Glycogen synthase kinase 3 (GSK-3), the well-known target protein for the treatment of diabetes and dementia, is a serine/threonine protein kinase which inhibits the activity of glycogen synthase (GS) by way of phosphorylation.

In the fatty tissue of mice suffering from fatty diabetes, the GSK-3β activity has been observed to be 2 fold higher than that of a normal mouse (H. Eldar-Finkelman, *Diabetes*, 48:1662-1666 (1999)) and patients during the second type diabetes are characterized by a high expression level of GSK-3β than normal (S. E. Nikoulina et al., *Diabetes*, 49: 263-171 (2000)). Also, the GSK-3β activity in the brain of a dementia patient is high (Yamaguchi H. et al., *Acta. N europathol.*, 92: 232-241 (1996)), and transgenic mice programmed to express GSK-3β in the brain have abnormal neurons caused by hyperphosphorylating tau of the neurofibrillary tangle which plays an important role in the dementia attack (Lucas J. J. et al., *EMBO J.* 20: 27-39 (2001)).

GSK-3 $\beta$  is further related to bipolar disorder which can be treated by lithium and valproic acid, well-known GSK-3 $\beta$  inhibitors (Elahi S. et al., *J. Infect. Dis.* 176: 217-226 (1997)).

Thus, there has existed a need to develop an effective inhibitor of  $GSK-3\beta$  for treating or preventing  $GSK-\beta$ -dependent diseases.

The present inventors have endeavored to develop an effective inhibitor of GSK-3 $\beta$ ; and have unexpectedly found that a compound containing a hydroxybenzoimidazole carboxylic amide moiety can inhibit the activity of GSK-3 $\beta$ , and therefore, can be used for treating or preventing GSK- $\beta$ -dependent diseases such as fatness, diabetes and dementia.

10

30

35

## **Summary of the Invention**

Accordingly, it is an object of the present invention to provide a GSK-3 $\beta$  inhibitor having high inhibitory activity against GSK-3 $\beta$ .

It is another object of the present invention to provide a process for preparing said inhibitor.

It is further object of the present invention to provide a pharmaceutical composition for inhibiting GSK-3 $\beta$  .

In accordance with one aspect of the present invention, there is provided a compound of formula (I), a pharmaceutically acceptable salt, hydrate, solvate or isomer thereof:

15 
$$(CH_2)_n$$
  $R^5$   $R^3$   $R^2$ 

wherein:

n is 0, 1, 2 or 3;

R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are each independently hydrogen, hydroxy, halogen or morpholin-1-yl-ethylamino;

R<sup>4</sup> and R<sup>5</sup> are each independently hydrogen;

linear or cyclic C<sub>1</sub>-C<sub>6</sub> alkyl optionally having one or more substituents, the carbon of the alkyl being optionally replaced with nitrogen, sulfur or oxygen, wherein the substituent is: hydroxy; halogen; alkyloxy; alkyl; amino; alkylamino; carboxyl; nitro; sulfonylamido; alkanesulfonyl; amido; an aromatic group optionally having one or more substituents selected from the group consisting of hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro, amido, dioxoisoindole and sulfonylamino; an aromatic group having one or more substituents selected from the group consisting of hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro and amido, the aromatic ring having nitrogen, sulfur or oxygen; or cyclic C<sub>3</sub>-C<sub>8</sub> alkyl optionally having one or more

10

15

20

25

30

35

substituents selected from the group consisting of hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro and amido;

an aromatic group optionally having one or more substituents, the aromatic ring having optional nitrogen, sulfur or oxygen, wherein the substituent is; hydroxy; halogen; alkyloxy; alkyl; amino; alkylamino; carboxyl; nitro; sulfonylamido, alkanesulfonyl; amido; or linear or cyclic C1-C<sub>6</sub> alkyl optionally having one or more substituents, the alkyl having an optional nitrogen, sulfur or oxygen linkage and the substituent of the alkyl being: hydroxy; halogen; alkyloxy; alkyl; amino; alkylamino; carboxyl; nitro; sulfonylamido, alkanesulfonyl; amido; an aromatic group optionally having one or more substituents selected from the group consisting of hydroxy; halogen; alkyloxy; alkyl; amino; alkylamino; carboxyl; nitro; amido; dioxoisoindole; and a sulfonylamino having an aromatic group substituted with hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro, sulfonylamido, alkanesulfonyl or amido; an aromatic group optionally having one or more substituents selected form the group consisting of hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro, sulfonylamide, alkanesulfonyl and amido, the aromatic ring containing nitrogen, sulfur or oxygen; or a cyclic C3-C8 alkyl optionally having one or more substituents selected from the group consisting of hydroxy, halogen, alkyloxy, alkyl, amino, alkylamino, carboxyl, nitro and amido; or

form, together with the -N- $(CH_2)_n$ - moiety to which they are attached, a nitrogen heterocycle optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub>, NO<sub>2</sub>, the heterocycle containing optional nitrogen or oxygen.

# **Detailed Description of the Invention**

Among the compounds of formula (I) of the present invention, the preferred are:

those wherein n,  $R^1$ ,  $R^2$  and  $R^3$  have the same meaning as defined previously;  $R^4$  and  $R^5$  are each independently hydrogen;

C<sub>1</sub>-C<sub>4</sub> alkyl optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub>, NO<sub>2</sub>, and an aromatic group, the aromatic group optionally having one or more substituents selected from the group consisting of OH, C<sub>1</sub>-C<sub>4</sub> alkyloxy, NH<sub>2</sub>, NO<sub>2</sub>, methanesulfonylamino, ethanesulfonylamino, tolunensulfonylamino and dioxoisoindole; cyclic C<sub>3</sub>-

10

15

20

30

35

 $C_8$  alkyl optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub> and NO<sub>2</sub>;  $C_1$ - $C_4$  alkyl carrying a morpholine or oxopyrolidine group which is optionally substituted with OH, NH<sub>2</sub>, NO<sub>2</sub> or - O-;  $C_1$ - $C_4$  alkyl or  $C_1$ - $C_4$  aminoalkyl carrying a pyrrol, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, isoxazole, oxazole, isotiazole, tiazolidine, tiazole, 1,2,5-oxadiazole, 1,2,3-oxadiazole, 1,2,5-thiodiazole, 1,2,3-thiodiazole, 1,3,4-oxadiazole, 1,3,4-thiodiazole, pyridine, pyrimidine or triazine group which is optionally having one or more substituents selected from the group consisting of Cl, OH, NH<sub>2</sub>, NO<sub>2</sub>,  $C_1$ - $C_4$  and phenyl;

cyclic  $C_3$ - $C_8$  alkyl optionally having one or more substituents selected from the group consisting of OH,  $NH_2$  and  $NO_2$ ;

an aromatic group optionally having one or more substituents selected from the group consisting of OH;  $NH_2$ ; hydroxyalkyl; aminoalkyl;  $NO_2$ ; and a  $C_1$ - $C_4$  alkyl group optionally having one or more substituents selected from the group consisting of OH,  $NH_2$ ,  $NO_2$ , methanesulfonylamino, ethanesulfonylamino, tolunensulfonylamino, dioxoisoindole and thiophensulfonylamino; or

form, together with the  $-N-(CH_2)_n$ - moiety to which they are attached, a nitrogen heterocycle optionally having one or more substituents selected from the group consisting of OH,  $NH_2$  and  $NO_2$ , the heterocycle containing 1 to 3 nitrogen, sulfur or oxygen atom.

In the present invention, the compounds of formula (I) as the below are most preferred:

25 those wherein n, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> have the same meaning as defined previously; R<sup>4</sup> and R<sup>5</sup> are each independently hydrogen;

C<sub>1</sub>-C<sub>4</sub> alkyl optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub>, NO<sub>2</sub>, morpholine, nitropyridineamino, pyridine, oxopyrolidin, imidazole optionally having a Cl, CH<sub>3</sub> or phenyl substituent; and phenyl optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub>, methoxy, NO<sub>2</sub>, methanesulfonylamino, ethanesulfonylamino, tolunensulfonylamino and dioxoisoindole;

cyclic  $C_3$ - $C_8$  alkyl optionally having one or more substituents selected from the group consisting of OH,  $NH_2$  and  $NO_2$ ;

phenyl optionally having one or more substituents selected from the group consisting of OH; NH<sub>2</sub>; NO<sub>2</sub>; and C<sub>1</sub>-C<sub>4</sub> alkyl optionally having a OH,

NH<sub>2</sub>, NO<sub>2</sub>, methanesulfonylamino, ethanesulfonylamino, tolunensulfonylamino, dioxoisoindole or thiophensulfonylamino substituent; or

form, together with -N-(CH<sub>2</sub>)<sub>n</sub>- moiety to which they are attached, a piperidine ring optionally having one or more substituents selected from the group consisting of OH, NH<sub>2</sub> and NO<sub>2</sub>.

Important compounds of the present invention are listed in Table 1 below.

10

5

Table 1

Com No.	n	$\mathbb{R}^1$	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
1	0	Н	Н	Н	Н	Н
2	0	Н	Н	Н	Н	Phenyl
3	0	Н	Н	Н	Н	4-hydroxyphenyl
4	0	Н	Н	Н	Н	4-aminophenyl
5	0	Н	Н	Н	Н	4-hydroxycyclohexyl
6	0	Н	Н	Н	Н	4-(hydroxymethyl)phenyl
7	0	Н	Н	Н	Н	4-(hydroxyethyl)phenyl
8	0	Н	Н	Н	Н	4-(aminoethyl)phenyl
9	0	Н	Н	Н	Н	4-(p-toluenesulfonamidylethyl)phenyl
10	0	Н	Н	Н	Н	4-(methanesulfonamidylethyl)phenyl
11	0	Н	Н	Н	Н	4-(phthalinidylethyl)phenyl
12	0	Н	Н	Н	Н	4-(2-thiophenylsulfonamidylethyl)phenyl
13	0	Н	Н	Н	Н	4-(ethansulfonamidylethyl)phenyl
14	0	Н	Н	Cl	Н	phenyl
15	0	Н	Н	Cl	Н	4-hydroxycyclohexyl

16	0	Н	H	Cl	Н	4-(p-toluenesulfonamidylethyl)phenyl
17	0	Н	Н	Cl	Н	4-(methanesulfonamidylethyl)phenyl
18	0	Н	Н	Cl	Н	4-(phthalinidylethyl)phenyl
19	0	Н	Н	Cl	Н	4-(2-thiophenylsulfonamidylethyl)phenyl
20	0	Н	Н	Cl	Н	4-(ethansulfonamidylethyl)phenyl
21	0	Cl	Н	Cl	Н	Н
22	0	Cl	Н	Cl	Н	Phenyl
23	0	CI	Н	Cl	Н	4-hydroxycyclohexyl
24	0	Cl	Н	Cl	Н	4-(aminoethyl)phenyl
25	0	Cl	Н	Cl	Н	4-aminophenyl
26	0	C1	Н	Cl	Н	4-(hydroxymethyl)phenyl
27	0	Cl	Н	Cl	Н	4-(hydroxyethyl)phenyl
28	0	Cl	Н	Cl	Н	4-(p-toluenesulfonamidylethyl)phenyl
29	0	C1	Н	Cl	Н	4-(methanesulfonamidylethyl)phenyl
30	0	Cl	Н	Cl	Н	4-(phthalinidylethyl)phenyl
31	0	Cl	Н	Cl	Н	4-(2-thiophenylsulfonamidylethyl)phenyl
32	0	C1	Н	Cl	Н	4-(ethansulfonamidylethyl)phenyl
33	0	Н	Н	F	Н	4-(methanesulfonamidylethyl)phenyl
34	0	Н	Н	F	н	4-(p-toluenesulfonamidylethyl)phenyl
35	0	Н	Н	F	н	4-(ethansulfonamidylethyl)phenyl
36	0	Н	Н	F	Н	4-morpholinophenyl
37	0	F	Н	F	Н	4-(methanesulfonamidylethyl)phenyl
38	0	F	Н	F	Н	4-(p-toluenesulfonamidylethyl)phenyl

39         0         F         H         F         H         4-(ethansulfonamidylethyl)phenyl           40         0         Cl         H         F         H         4-(p-toluenesulfonamidylethyl)phenyl           41         0         Cl         H         F         H         4-(ethansulfonamidylethyl)phenyl           42         0         Cl         H         F         H         4-(ethansulfonamidylethyl)phenyl           43         0         H         Cl         F         H         4-(ethansulfonamidylethyl)phenyl           44         0         H         Cl         F         H         4-(ethansulfonamidylethyl)phenyl           45         0         H         Cl         F         H         4-(ethansulfonamidylethyl)phenyl           46         0         H         Cl         F         H         4-(ethansulfonamidylethyl)phenyl           46         0         H         H         H         4-(ethansulfonamidylethyl)phenyl           47         0         H         H         H         4-(methanesulfonamidylethyl)phenyl           48         0         Cl         H         Cl         R-(p-toluenesulfonamidylethyl)phenyl           48         0 <t< th=""><th></th><th></th><th></th><th></th><th></th><th></th><th></th></t<>							
41         0         Cl         H         F         H         4-(methanesulfonamidylethyl)phenyl           42         0         Cl         H         F         H         4-(ethansulfonamidylethyl)phenyl           43         0         H         Cl         F         H         4-(ethansulfonamidylethyl)phenyl           44         0         H         Cl         F         H         4-(ethansulfonamidylethyl)phenyl           45         0         H         Cl         F         H         4-(methanesulfonamidylethyl)phenyl           46         0         H         H         H         A-(methanesulfonamidylethyl)phenyl           46         0         H         H         H         4-(methanesulfonamidylethyl)phenyl           46         0         H         H         H         4-(methanesulfonamidylethyl)phenyl           48         0         Cl         H         H         H         4-(methanesulfonamidylethyl)phenyl           48         0         Cl         H         Cl         R*, R*5 = piperidinyl           48         0         Cl         H         H         4-nitrophenyl           50         1         H         H         H         H	39	0	F	Н	F	Н	4-(ethansulfonamidylethyl)phenyl
42         0         Cl         H         F         H         4-(ethansulfonamidylethyl)phenyl           43         0         H         Cl         F         H         4-(ethansulfonamidylethyl)phenyl           44         0         H         Cl         F         H         4-(ethansulfonamidylethyl)phenyl           45         0         H         Cl         F         H         4-(methanesulfonamidylethyl)phenyl           46         0         H         H         H         H         4-(methanesulfonamidylethyl)phenyl           46         0         H         H         H         4-(methanesulfonamidylethyl)phenyl           46         0         H         H         H         4-(methanesulfonamidylethyl)phenyl           46         0         H         H         H         4-(methanesulfonamidylethyl)phenyl           48         0         Cl         H         H         4-(methanesulfonamidylethyl)phenyl           48         0         Cl         H         Cl         R*4, R*5 = piperidinyl           48         0         Cl         H         H         4-aminophenyl           50         1         H         H         H         H         4-mitro	40	0	Cl	Н	F	Н	4-(p-toluenesulfonamidylethyl)phenyl
43         0         H         Cl         F         H         4-(p-toluenesulfonamidylethyl)phenyl           44         0         H         Cl         F         H         4-(ethansulfonamidylethyl)phenyl           45         0         H         Cl         F         H         4-(methanesulfonamidylethyl)phenyl           46         0         H         H         H         R <sup>4</sup> , R <sup>5</sup> = piperidinyl           47         0         H         H         Cl         R <sup>4</sup> , R <sup>5</sup> = piperidinyl           48         0         Cl         H         Cl         R <sup>4</sup> , R <sup>5</sup> = piperidinyl           49         1         H         H         H         4-nitrophenyl           50         1         H         H         H         4-aminophenyl           51         1         H         H         H         4-nitrophenyl           52         1         H         H         Cl         H         4-aminophenyl           53         1         H         H         Cl         H         4-aminophenyl           54         1         H         Cl         H         4-nitrophenyl           56         1         Cl         H	41	0	Cl	Н	F	H	4-(methanesulfonamidylethyl)phenyl
44         0         H         Cl         F         H         4-(ethansulfonamidylethyl)phenyl           45         0         H         Cl         F         H         4-(methanesulfonamidylethyl)phenyl           46         0         H         H         H         R <sup>4</sup> , R <sup>5</sup> = piperidinyl           47         0         H         H         Cl         R <sup>4</sup> , R <sup>5</sup> = piperidinyl           48         0         Cl         H         Cl         R <sup>4</sup> , R <sup>5</sup> = piperidinyl           49         1         H         H         H         4-nitrophenyl           50         1         H         H         H         4-aminophenyl           51         1         H         H         H         Phenyl           52         1         H         H         Cl         H         4-nitrophenyl           53         1         H         H         Cl         H         4-aminophenyl           54         1         H         H         Cl         H         4-aminophenyl           55         1         Cl         H         Cl         H         4-nitrophenyl           56         1         Cl         H         H </td <td>42</td> <td>0</td> <td>Cl</td> <td>Н</td> <td>F</td> <td>Н</td> <td>4-(ethansulfonamidylethyl)phenyl</td>	42	0	Cl	Н	F	Н	4-(ethansulfonamidylethyl)phenyl
45 0 H Cl F H 4-(methanesulfonamidylethyl)phenyl 46 0 H H H H R <sup>4</sup> , R <sup>5</sup> = piperidinyl 47 0 H H Cl R <sup>4</sup> , R <sup>5</sup> = piperidinyl 48 0 Cl H Cl R <sup>4</sup> , R <sup>5</sup> = piperidinyl 49 1 H H H H H 4-nitrophenyl 50 1 H H H H H F Phenyl 51 1 H H H H H Phenyl 52 1 H H Cl H Phenyl 53 1 H H Cl H 4-nitrophenyl 54 1 H H Cl H 4-nitrophenyl 55 1 Cl H Cl H 4-nitrophenyl 56 1 Cl H Cl H 4-nitrophenyl 57 2 H H H H H Phenyl 58 2 H H H H H A-nitrophenyl 59 2 H H H H H A-nitrophenyl 59 2 H H H H H A-nitrophenyl 59 2 H H H H H A-nitrophenyl	43	0	Н	Cl	F	Н	4-(p-toluenesulfonamidylethyl)phenyl
46         0         H         H         H         H         R <sup>4</sup> , R <sup>5</sup> = piperidinyl           47         0         H         H         Cl         R <sup>4</sup> , R <sup>5</sup> = piperidinyl           48         0         Cl         H         Cl         R <sup>4</sup> , R <sup>5</sup> = piperidinyl           49         1         H         H         H         H         4-nitrophenyl           50         1         H         H         H         H         4-aminophenyl           51         1         H         H         H         Phenyl           52         1         H         H         Cl         H         4-nitrophenyl           53         1         H         H         Cl         H         4-aminophenyl           54         1         H         H         Cl         H         4-aminophenyl           55         1         Cl         H         Cl         H         4-nitrophenyl           56         1         Cl         H         H         H         H         4-hydroxyphenyl           58         2         H         H         H         H         4-nitrophenyl           59         2         H <td>44</td> <td>0</td> <td>Н</td> <td>Cl</td> <td>F</td> <td>Н</td> <td>4-(ethansulfonamidylethyl)phenyl</td>	44	0	Н	Cl	F	Н	4-(ethansulfonamidylethyl)phenyl
47         0         H         H         Cl         R <sup>4</sup> , R <sup>5</sup> = piperidinyl           48         0         Cl         H         Cl         R <sup>4</sup> , R <sup>5</sup> = piperidinyl           49         1         H         H         H         H         4-nitrophenyl           50         1         H         H         H         H         4-aminophenyl           51         1         H         H         H         H         phenyl           52         1         H         H         Cl         H         4-nitrophenyl           53         1         H         H         Cl         H         4-aminophenyl           54         1         H         H         Cl         H         4-aminophenyl           55         1         Cl         H         Cl         H         4-nitrophenyl           56         1         Cl         H         Cl         H         4-nitrophenyl           57         2         H         H         H         H         4-nitrophenyl           58         2         H         H         H         H         4-nitrophenyl	45	0	Н	Cl	F	Н	4-(methanesulfonamidylethyl)phenyl
48         0         Cl         H         Cl         R <sup>4</sup> , R <sup>5</sup> = piperidinyl           49         1         H         H         H         H         4-nitrophenyl           50         1         H         H         H         H         4-aminophenyl           51         1         H         H         H         Phenyl           52         1         H         H         Cl         H         Phenyl           53         1         H         H         Cl         H         4-nitrophenyl           54         1         H         H         Cl         H         phenyl           55         1         Cl         H         Cl         H         4-nitrophenyl           56         1         Cl         H         H         H         Phenyl           57         2         H         H         H         H         4-nitrophenyl           58         2         H         H         H         H         4-nitrophenyl           59         2         H         H         H         H         4-nitrophenyl	46	0	H	Н	Н		$R^4$ , $R^5$ = piperidinyl
49         1         H	47	0	Н	Н	Cl		$R^4$ , $R^5$ = piperidinyl
50         1         H         H         H         H         H         H         H         H         H         H         H         Phenyl           51         1         H         H         H         H         Phenyl         Phenyl           52         1         H         H         Cl         H         Phenyl           53         1         H         H         Cl         H         4-nitrophenyl           54         1         H         H         Cl         H         Phenyl           55         1         Cl         H         Cl         H         Phenyl           56         1         Cl         H         Cl         H         Phenyl           57         2         H         H         H         H         Phenyl           58         2         H         H         H         H         4-nitrophenyl           59         2         H         H         H         H         4-nitrophenyl	48	0	Cl	Н	C1		$R^4$ , $R^5$ = piperidinyl
51         1         H         H         H         H         Phenyl           52         1         H         H         Cl         H         phenyl           53         1         H         H         Cl         H         4-nitrophenyl           54         1         H         H         Cl         H         phenyl           55         1         Cl         H         Cl         H         phenyl           56         1         Cl         H         Cl         H         4-nitrophenyl           57         2         H         H         H         H         4-hydroxyphenyl           58         2         H         H         H         H         4-nitrophenyl	49	1	Н	Н	Н	Н	4-nitrophenyl
52         1         H         H         Cl         H         phenyl           53         1         H         H         Cl         H         4-nitrophenyl           54         1         H         H         Cl         H         4-aminophenyl           55         1         Cl         H         Cl         H         phenyl           56         1         Cl         H         Cl         H         4-nitrophenyl           57         2         H         H         H         H         4-hydroxyphenyl           58         2         H         H         H         H         4-nitrophenyl           59         2         H         H         H         H         4-nitrophenyl	50	1	Н	Н	Н	Н	4-aminophenyl
53         1         H         H         Cl         H         4-nitrophenyl           54         1         H         H         Cl         H         4-aminophenyl           55         1         Cl         H         Cl         H         phenyl           56         1         Cl         H         Cl         H         4-nitrophenyl           57         2         H         H         H         phenyl           58         2         H         H         H         4-hydroxyphenyl           59         2         H         H         H         H         4-nitrophenyl	51	1	Н	Н	Н	Н	phenyl
54         1         H         H         Cl         H         4-aminophenyl           55         1         Cl         H         Cl         H         phenyl           56         1         Cl         H         Cl         H         4-nitrophenyl           57         2         H         H         H         phenyl           58         2         H         H         H         4-hydroxyphenyl           59         2         H         H         H         4-nitrophenyl	52	1	Н	Н	Cl	Н	phenyl
55         1         Cl         H         Cl         H         phenyl           56         1         Cl         H         Cl         H         4-nitrophenyl           57         2         H         H         H         phenyl           58         2         H         H         H         4-nitrophenyl           59         2         H         H         H         4-nitrophenyl	53	1	Н	Н	Cl	Н	4-nitrophenyl
56         1         Cl         H         Cl         H         4-nitrophenyl           57         2         H         H         H         phenyl           58         2         H         H         H         4-nitrophenyl           59         2         H         H         H         4-nitrophenyl	54	1	Н	Н	Cl	Н	4-aminophenyl
57         2         H         H         H         H         H         phenyl           58         2         H         H         H         H         4-hydroxyphenyl           59         2         H         H         H         H         4-nitrophenyl	55	1	Cl	Н	Cl	Н	phenyl
58         2         H         H         H         H         4-hydroxyphenyl           59         2         H         H         H         4-nitrophenyl	56	1	Cl	Н	Cl	Н	4-nitrophenyl
59 2 H H H H 4-nitrophenyl	57	2	Н	Н	Н	Н	phenyl
	58	2	Н	Н	Н	Н	4-hydroxyphenyl
60 2 H H H H A aminophenyl	59	2	Н	Н	Н	Н	4-nitrophenyl
4-animophenyi	60	2	Н	Н	Н	Н	4-aminophenyl
61 2 H H H H amino	61	2	Н	Н	Н	Н	amino

62         2         H         H         H         H         4-hydroxy-3-methoxyphenyl           63         2         H<					<del>,</del>		
64         2         H	62	2	Н	H	Н	Н	4-hydroxy-3-methoxyphenyl
65         2         H	63	2	H	H	Н	Н	3-hydroxy-4-methoxyphenyl
66         2         H         H         H         H         H         H         H         4-morpholinyl           67         2         H         H         H         H         4-phthlimidophenyl           68         2         H         H         H         H         4-(ethanesulfonamidyl)phenyl           69         2         H         H         H         H         4-nitro-2-pyridinylamino           70         2         H         H         H         H         2-pyridyl           71         2         H         H         Cl         H         4-nitro-2-pyridinylamino           72         2         H         H         Cl         H         4-nitrophenyl           73         2         H         H         Cl         H         4-aminophenyl           74         2         H         H         Cl         H         4-(methanesulfonamidyl)phenyl           75         2         H         H         Cl         H         4-(p-toluenesulfonamidyl)phenyl           76         2         H         H         Cl         H         N-morpholinyl           78         2         H         H	64	2	Н	Н	Н	Н	4-(methanesulfonamidyl)phenyl
67         2         H         H         H         H         4-phthlimidophenyl           68         2         H         H         H         H         4-(ethanesulfonamidyl)phenyl           69         2         H         H         H         H         4-nitro-2-pyridinylamino           70         2         H         H         H         H         2-pyridyl           71         2         H         H         Cl         H         phenyl           72         2         H         H         Cl         H         4-nitrophenyl           73         2         H         H         Cl         H         4-aminophenyl           74         2         H         H         Cl         H         4-introphenyl           75         2         H         H         Cl         H         4-introphenyl           76         2         H         H         Cl         H         4-(p-toluenesulfonamidyl)phenyl           77         2         H         H         Cl         H         N-morpholinyl           79         2         H         H         Cl         H         4-phthalimidophenyl	65	2	H	Н	Н	Н	4-(p-toluenesulfonamidyl)phenyl
68         2         H         Description         Description         Description         H         H         H         H         H         H         H         H         H         H         H         H         Description         Descript	66	2	H	Н	Н	Н	4-morpholinyl
69         2         H	67	2	Н	Н	Н	Н	4-phthlimidophenyl
70         2         H         H         H         H         H         2-pyridyl           71         2         H         H         Cl         H         phenyl           72         2         H         H         Cl         H         4-nitrophenyl           73         2         H         H         Cl         H         4-aminophenyl           74         2         H         H         Cl         H         4-hydroxyphenyl           75         2         H         H         Cl         H         4-(methanesulfonamidyl)phenyl           76         2         H         H         Cl         H         4-(p-toluenesulfonamidyl)phenyl           77         2         H         H         Cl         H         N-morpholinyl           78         2         H         H         Cl         H         N-morpholinyl           79         2         H         H         Cl         H         4-phthalimidophenyl           80         2         H         H         Cl         H         4-(ethanesulfonamidyl)phenyl           81         2         H         H         Cl         H         4-nitro-2-pyridin	68	2	Н	H	Н	Н	4-(ethanesulfonamidyl)phenyl
71         2         H         H         Cl         H         phenyl           72         2         H         H         Cl         H         4-nitrophenyl           73         2         H         H         Cl         H         4-aminophenyl           74         2         H         H         Cl         H         4-hydroxyphenyl           75         2         H         H         Cl         H         4-(methanesulfonamidyl)phenyl           76         2         H         H         Cl         H         4-(p-toluenesulfonamidyl)phenyl           77         2         H         H         Cl         H         3-hydroxy-4-methoxyphenyl           78         2         H         H         Cl         H         N-morpholinyl           79         2         H         H         Cl         H         4-phthalimidophenyl           80         2         H         H         Cl         H         4-(ethanesulfonamidyl)phenyl           81         2         H         H         Cl         H         4-nitro-2-pyridinylamino           82         2         H         H         Cl         H         2-pyridy	69	2	Н	H	Н	Н	4-nitro-2-pyridinylamino
72         2         H         H         Cl         H         4-nitrophenyl           73         2         H         H         Cl         H         4-aminophenyl           74         2         H         H         Cl         H         4-hydroxyphenyl           75         2         H         H         Cl         H         4-(methanesulfonamidyl)phenyl           76         2         H         H         Cl         H         4-(p-toluenesulfonamidyl)phenyl           77         2         H         H         Cl         H         3-hydroxy-4-methoxyphenyl           78         2         H         H         Cl         H         N-morpholinyl           79         2         H         H         Cl         H         4-phthalimidophenyl           80         2         H         H         Cl         H         4-(ethanesulfonamidyl)phenyl           81         2         H         H         Cl         H         4-nitro-2-pyridinylamino           82         2         H         H         Cl         H         2-pyridyl	70	2	Н	H	Н	Н	2-pyridyl
73         2         H         H         Cl         H         4-aminophenyl           74         2         H         H         Cl         H         4-hydroxyphenyl           75         2         H         H         Cl         H         4-(methanesulfonamidyl)phenyl           76         2         H         H         Cl         H         4-(p-toluenesulfonamidyl)phenyl           77         2         H         H         Cl         H         3-hydroxy-4-methoxyphenyl           78         2         H         H         Cl         H         N-morpholinyl           79         2         H         H         Cl         H         4-phthalimidophenyl           80         2         H         H         Cl         H         4-(ethanesulfonamidyl)phenyl           81         2         H         H         Cl         H         4-nitro-2-pyridinylamino           82         2         H         H         Cl         H         2-pyridyl	71	2	Н	Н	CI	Н	phenyl
74         2         H         H         Cl         H         4-hydroxyphenyl           75         2         H         H         Cl         H         4-(methanesulfonamidyl)phenyl           76         2         H         H         Cl         H         4-(p-toluenesulfonamidyl)phenyl           77         2         H         H         Cl         H         3-hydroxy-4-methoxyphenyl           78         2         H         H         Cl         H         N-morpholinyl           79         2         H         H         Cl         H         4-phthalimidophenyl           80         2         H         H         Cl         H         4-(ethanesulfonamidyl)phenyl           81         2         H         H         Cl         H         4-nitro-2-pyridinylamino           82         2         H         H         Cl         H         2-pyridyl	72	2	Н	H	Cl	Н	4-nitrophenyl
75 2 H H Cl H 4-(methanesulfonamidyl)phenyl  76 2 H H Cl H 4-(p-toluenesulfonamidyl)phenyl  77 2 H H Cl H 3-hydroxy-4-methoxyphenyl  78 2 H H Cl H N-morpholinyl  79 2 H H Cl H 4-(ethanesulfonamidyl)phenyl  80 2 H H Cl H 4-(ethanesulfonamidyl)phenyl  81 2 H H Cl H 4-nitro-2-pyridinylamino  82 2 H H Cl H 2-pyridyl	73	2	Н	Н	Cl	Н	4-aminophenyl
76 2 H H Cl H 4-(p-toluenesulfonamidyl)phenyl 77 2 H H Cl H 3-hydroxy-4-methoxyphenyl 78 2 H H Cl H N-morpholinyl 79 2 H H Cl H 4-phthalimidophenyl 80 2 H H Cl H 4-(ethanesulfonamidyl)phenyl 81 2 H H Cl H 4-nitro-2-pyridinylamino 82 2 H H Cl H 2-pyridyl	74	2	Н	Н	Cl	Н	4-hydroxyphenyl
77 2 H H Cl H 3-hydroxy-4-methoxyphenyl  78 2 H H Cl H N-morpholinyl  79 2 H H Cl H 4-phthalimidophenyl  80 2 H H Cl H 4-(ethanesulfonamidyl)phenyl  81 2 H H Cl H 4-nitro-2-pyridinylamino  82 2 H H Cl H 2-pyridyl	75	2	Н	H	Cl	Н	4-(methanesulfonamidyl)phenyl
78         2         H         H         Cl         H         N-morpholinyl           79         2         H         H         Cl         H         4-phthalimidophenyl           80         2         H         H         Cl         H         4-(ethanesulfonamidyl)phenyl           81         2         H         H         Cl         H         4-nitro-2-pyridinylamino           82         2         H         H         Cl         H         2-pyridyl	76	2	Н	Н	Cl	Н	4-(p-toluenesulfonamidyl)phenyl
79         2         H         H         Cl         H         4-phthalimidophenyl           80         2         H         H         Cl         H         4-(ethanesulfonamidyl)phenyl           81         2         H         H         Cl         H         4-nitro-2-pyridinylamino           82         2         H         H         Cl         H         2-pyridyl	77	2	Н	Н	Cl	н	3-hydroxy-4-methoxyphenyl
80 2 H H Cl H 4-(ethanesulfonamidyl)phenyl 81 2 H H Cl H 4-nitro-2-pyridinylamino 82 2 H H Cl H 2-pyridyl	78	2	Н	Н	Cl	Н	N-morpholinyl
81 2 H H Cl H 4-nitro-2-pyridinylamino  82 2 H H Cl H 2-pyridyl	79	2	Н	Н	Cl	Н	4-phthalimidophenyl
82 2 H H Cl H 2-pyridyl	80	2	Н	Н	Cl	Н	4-(ethanesulfonamidyl)phenyl
22 O II II Z-pyridyi	81	2	Н	Н	Cl	н	4-nitro-2-pyridinylamino
83 2 H H Cl H 4-imidazolyl	82	2	Н	Н	Cl	Н	2-pyridyl
- Initiazolyi	83	2	Н	Н	Cl	Н	4-imidazolyl
84 2 H H Cl H 4-hydroxyphenyl	84	2	Н	Н	Cl	Н	4-hydroxyphenyl

	<del></del>			,		
85	2	Н	Н	Cl	Н	4-acetylamino-2-pyridylamino
86	2	Н	Н	Cl	Н	4-(4-methylpiperazin-1-yl- acetylamino)phenyl
87	2	Н	Н	CI	Н	4-(4-ethylpiperazin-1-yl-acetylamino)phenyl
88	2	Н	Н	Cl	Н	4-(dimethylaminoacetylamino)phenyl
89	2	Н	H	Cl	Н	4-(diethylaminoacetylamino)phenyl
90	2	Н	Н	Cl	Н	4-aminophenyl
91	2	Н	H	Cl	Н	4-amino-2-pyridylamino
92	2	Н	Н	Cl	Н	4-(morpholin-4-yl-acetylamino)phenyl
93	2	Н	Н	Cl	Н	4-(N,N-dimethylamino)phenyl
94	2	Н	Н	Cl	Н	4-(morpholin-4-yl-ethoxy)phenyl
95	2	H	H	Cl	Н	4-(4-methylpiperazin-1-yl-ethoxy)phenyl
96	2	Н	Н	Cl	Н	2-hydroxyphenyl
97	2	H	Н	Cl	н	2-methoxyphenyl
98	2	H	Н	Cl	Н	3-bromophenyl
99	2	Cl	Н	Cl	Н	phenyl
100	2	Cl	Н	Cl	Н	4-nitrophenyl
101	2	Cl	Н	Cl	н	4-hydroxy-3-methoxyphenyl
102	2	C1	Н	Cl	Н	3-hydroxy-4-methoxyphenyl
103	2	Cl	Н	Cl	Н	amino
104	2	Cl	Н	Cl	Н	4-hydroxyphenyl
105	2	Cl	Н	Cl	н	4-(p-toluenesulfonamidyl)phenyl
106	2	Cl	Н	Cl	Н	4-(methanesulfonamidyl)phenyl

	т	_	,			
107	2	Cl	Н	CI	Н	4-phthlimidophenyl
108	2	Cl	Н	Cl	Н	4-morpholinyl
109	2	Cl	Н	Cl	Н	4-(ethanesulfonamidyl)phenyl
110	2	Cl	Н	CI	Н	4-nitro-2-pyridinylamino
111	2	Cl	Н	Cl	Н	2-pyridyl
112	2	Cl	Н	Cl	Н	4-(acetylamino)phenyl
113	2	Cl	Н	CI	Н	4-(pentanoylamino)phenyl
114	2	Н	Н	F	Н	4-(methanesulfonamidyl)phenyl
115	2	Н	Н	F	Н	4-(p-toluenesulfonamidyl)phenyl
116	2	Н	Н	F	Н	4-(ethanesulfonamidyl)phenyl
117	2	Н	Н	F	Н	4-(acetylamino)phenyl
118	2	Н	Н	F	Н	4-methylpiperazin-1-yl
119	2	Н	Н	F	Н	4-morpholin-1-yl
120	2	Н	Н	F	Н	4-(pentanoylamino)phenyl
121	2	Н	Н	F	Н	4-hydroxyphenyl
122	2	Н	Н	F	Н	4-nitro-2-pyridinylamino
123	2	Н	Н	F	Н	4-(methanesulfonylamino-2-pyridyl)amino
124	2	Н	Н	F	Н	4-(p-toluenesulfonylamino-2-pyridyl)amino
125	2	Н	Н	F	Н	4-imidazolyl
126	2	Н	Н	F	Н	4-acetylamino-2-pyridylamino
127	2	Н	Н	F	Н	4-(4-methylpiperazin-1-yl-
128	2	н	Н	F	Н	acetylamino)phenyl 4-(4-ethylpiperazin-1-yl-acetylamino)phenyl

1 1			<u> </u>		т	
129	2	H	Н	F	Н	4-(dimethylaminoacetylamino)phenyl
130	2	Н	Н	F	Н	4-(diethylaminoacetylamino)phenyl
131	2	Н	Н	F	Н	4-aminophenyl
132	2	Н	Н	F	Н	4-morpholinophenyl
133	2	Н	Н	F	Н	4-(3-dimethylaminopyrrolidin-1-yl)phenyl
134	2	Н	Н	F	Н	4-(morpholin-4-yl-acetylamino)phenyl
135	2	Н	Н	F	Н	4-(N,N-dimethylamino)phenyl
136	2	Н	Н	F	н	4-(morpholin-4-yl-ethoxy)phenyl
137	2	Н	Н	F	Н	2-hydroxyphenyl
138	2	Н	Н	F	Н	2-methoxyphenyl
139	2	Н	Н	F	Н	3-bromophenyl
140	2	F	Н	F	Н	4-(methanesulfonamidyl)phenyl
141	2	F	Н	F	Н	4-(p-toluenesulfonamidyl)phenyl
142	2	F	Н	F	н	4-(ethanesulfonamidyl)phenyl
143	2	Cl	Н	F	Н	4-(methanesulfonamidyl)phenyl
144	2	C1	Н	F	Н	4-(p-toluenesulfonamidyl)phenyl
145	2	Cl	Н	F	Н	4-(ethanesulfonamidyl)phenyl
146	2	Cl	Н	F	Н	4-(acetylamino)phenyl
147	2	Cl	Н	F	Н	4-morpholin-1-yl
148	2	Cl	Н	F	Н	4-methylpiperazin-1-yl
149	2	C1	Н	F	Н	4-(pentanoylamino)phenyl
150	2	C1	Н	F	Н	4-hydroxyphenyl
151	2	Cl	Н	F	Н	4-nitro-2-pyridinylamino

	τ	1	<del></del>	<del></del>		T
152	2	CI	Н	F	Н	4-(methanesulfonylamino-2-pyridyl)amino
153	2	Cl	Н	F	Н	4-(p-toluenesulfonylamino-2-pyridyl)amino
154	2	Cl	Н	F	Н	4-imidazolyl
155	2	Cl	Н	F	Н	4-acetylamino-2-pyridylamino
156	2	Cl	Н	F	Н	4-(4-methylpiperazin-1-yl- acetylamino)phenyl
157	2	Cl	Н	F	Н	4-(4-ethylpiperazin-1-yl-acetylamino)phenyl
158	2	Cl	Н	F	Н	4-(dimethylaminoacetylamino)phenyl
159	2	Cl	Н	F	Н	4-(diethylaminoacetylamino)phenyl
160	2	Н	Cl	F	Н	4-(p-toluenesulfonamidyl)phenyl
161	2	Н	Cl	F	Н	4-(methanesulfonamidyl)phenyl
162	3	Н	Н	Н	Н	methyl
163	3	Н	Н	Н	Н	amino
164	3	H	Н	H	Н	2-oxopyrrolidin-1-yl
165	3	Н	Н	Н	Н	1-imidazolyl
166	3	Н	Н	H	н	4-N-morpholinyl
167	3	Н	Н	H	Н	2-methylimidazol-1-yl
168	3	Н	Н	Cl	н	methyl
169	3	Н	Н	Cl	Н	2-oxopyrrolidin-1-yl
170	3	Н	Н	Cl	Н	1-imidazolyl
171	3	Н	Н	Cl	Н	4-morpholinyl
172	3	Н	Н	Cl	Н	2-phenylimidazol-1-yl
173	3	Н	Н	Cl	Н	4-methylimidazol-1-yl

174	3	Н	Н	Cl	Н	4,5-dichloroimidazol-1-yl
175	3	Н	Н	Cl	Н	2-methylimidazol-1-yl
176	3	Cl	Н	Cl	Н	methyl
177	3	Cl	Н	Cl	Н	2-oxopyrrolidin-1-yl
178	3	Cl	Н	Cl	Н	1-imidazolyl
179	3	Cl	Н	Cl	Н	4-morpholin-yl
180	3	Cl	Н	Cl	Н	2-phenylimidazol-1-yl
181	3	Cl	Н	Cl	Н	4-methylimidazol-1-yl
182	3	Cl	Н	Cl	Н	4,5-dichloroimidazol-1-yl
183	3	Cl	Н	Cl	Н	2-methylimidazol-1-yl
184	3	Cl	Н	Cl	Н	2-isopropylimidazol-1-yl
185	3	Н	Н	F	Н	1-imidazolyl
186	3	Н	Н	F	Н	2-isopropylimidazol-1-yl
187	3	Н	Н	F	Н	4-methylimidazol-1-yl
188	3	Н	Н	F	Н	2-methylimidazol-1-yl
189	3	Н	Н	F	Н	2-ethylimidazol-1-yl
190	3	Н	Н	F	Н	4,5-dichloroimidazol-1-yl
191	3	F	Н	F	Н	2-isopropylimidazol-1-yl
192	3	F	Н	F	н	1-imidazolyl
193	3	F	Н	F	Н	4-methylimidazol-1-yl
194	3	F	Н	F	H	4,5-dichloroimidazol-1-yl
195	3	F	Н	F	Н	2-methylimidazol-1-yl
196	3	F	Н	F	Н	2-ethylimidazol-1-yl

		1		1	т	
197	3	F	Н	F	H	4,5-dichloroimidazol-1-yl
198	3	Cl	Н	F	Н	1-imidazolyl
199	3	Cl	Н	F	Н	4-methylimidazol-1-yl
200	3	CI	Н	F	Н	4,5-dichloroimidazol-1-yl
201	3	Cl	Н	F	Н	2-methylimidazol-1-yl
202	3	Н	Cl	F	Н	4-methylimidazol-1-yl
203	3	Н	Cl	F	Н	1-imidazolyl
204	3	$R^3 =$	mc	nd R <sup>4</sup> : orpholi ylamin	n-1-	4,5-dichloroimidazol-1-yl

The inventive compound (except for the compound wherein R<sup>3</sup> is morpholin-1-yl-ethylamino) of formula (Ia) may be prepared as in Scheme 1.

### 5 Scheme I

10

15

20

25

30

wherein, p-TSA is p-toluenesulfonic acid, DMF is dimethylformamide, THF is tetrahydrofuran, TFA is trifluoroacetic acid, EDCI is ethyl-dimethylaminopropyl-carbodiimide hyrochloride, DMAP is 4-dimethylaminoprydine, HOBt is N-hydroxybezotriazole, n,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $R^5$  have the same meaning as defined previously.

As shown in Scheme I, the compound of formula (Ia) can be prepared by reacting 3-amino-4-methoxy benzoic acid (compound II) and an alcohol (e.g., methanol or ethanol) to obtain compound (III); adding anhydrous ptoluenesulfonic acid and benzonitrile to the compound (III) thus obtained, refluxing the mixture at 80 to 200 °C, adding NaOCl thereto at room temperature and purifying by silica gel column chromatography to obtain compound (IV); dissolving the compound (IV) thus obtained in an alcohol (e.g., methanol or ethanol), adding an aqueous alkali solution (Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, K<sub>2</sub>CO<sub>2</sub> or KHCO<sub>3</sub> solution) thereto and refluxing the mixture to obtain compound (V); dissolving the compound (V) thus obtained in an organic solvent, e.g., toluene, adding a Lewis acid (e.g., AlCl<sub>3</sub> or BBr<sub>3</sub>) thereto and refluxing the mixture to obtain compound (VI); dissolving the compound (V) thus obtained in an alcohol, adding a strong acid, nitric acid or sulfuric acid, thereto at room temperature and refluxing the mixture to obtain compound (VII); dissolving the compound (VII) thus obtained and (4bromomethylphenoxy)-methyl polystyrene Wang resin in an organic solvent, e.g., DMF, THF or chloroform, adding a base (CsCO3, Na2CO3, NaHCO3, K<sub>2</sub>CO<sub>3</sub> or KHCO<sub>3</sub>) and KI thereto (1:3:3:3) and stirring the mixture at 50 to 60 °C for 1 to 24 hours to obtain compound (VIII); dissolving the compound (VIII) thus obtained in an organic solvent, adding an alcohol solution of an alkali hydroxide (e.g., LiOH, NaOH or KOH) thereto and refluxing the mixture to obtain compound (IX); dissolving the compound (IX) thus obtained in an organic solvent, adding R<sup>4</sup>N(CH<sub>2</sub>)<sub>n</sub>R<sup>5</sup> and a coupling agent (e.g., EDCI/DMAP/HOBt, DCC or pyBop) thereto and stirring the mixture at room temperature to obtain compound (X); and dissolving the compound (X) thus obtained in CH<sub>2</sub>Cl<sub>2</sub>, adding trifluoroacetic acid thereto and stirring the mixture at room temperature to obtain compound (Ia).

The inventive compound (wherein R<sup>3</sup> is morpholin-1-yl-ethylamino) represented to formula (Ib) may be prepared, as in Scheme II.

30

35

#### Scheme II

As shown in Scheme II, the compound of formula (Ib) can be prepared by reacting 3-amino-4-methoxy benzoic acid (compound II) and an alcohol (e.g., methanol or ethanol) to obtain compound (III), adding ptoluenesulfonic acid, benzene and 4-nitrobezonitrile thereto, refluxing the mixture at 80 to 200 °C, adding NaOCl thereto at room temperature and purifying by silica gel column chromatography to obtain compound (XI); dissolving the compound (XI) thus obtained in an organic solvent, adding an aqueous alkali solution (e.g., Na<sub>2</sub>CO<sub>3</sub> solution) thereto, refluxing the mixture and purifying by silica gel column chromatography to obtain compound (XII); dissolving the compound (XII) thus obtained in an alcohol, adding Pd/C thereto and refluxing the mixture to obtain compound (XIII); dissolving the compound (XIII) thus obtained in an organic solvent, adding a CsCO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, NaHCO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub> or KHCO<sub>3</sub>), base chloroethylmorphine and potassium iodide thereto and stirring the mixture at room temperature to obtain compound (XIV); dissolving the compound (XIV) obtained thus in an organic solvent, adding an alkali hydrate, stirring the mixture at room temperature to obtain compound (XV); dissolving the compound (XV) thus obtained in an organic solvent, adding 4,5-dichloro-1-(3-aminoprophyl)imidazole and a coupling agent (e.g., EDCI, DMAP or HOBt), stirring the mixture at room temperature and purifying by silica gel

column chromatography to obtain compound (XVI); and dissolving the compound (XVI) thus obtained in MC, adding a Lewis acid thereto, stirring the mixture, concentrating the resulting solution under a reduced pressure and purifying by silica gel column chromatography to obtain compound (Ib).

5

10

15

20

25

30

35

A salt, hydrate, solvate and isomer of the inventive compound of formula (I) may be prepared by employing any of the known methods. The inventive compound of formula (I), a salt, hydrate, solvate or isomer thereof may used for the treatment of GSK-3 $\beta$ -dependent diseases including fatness, diabetes and dementia, by way of inhibiting GSK-3 $\beta$  activity, the inventive compound having an IC<sub>50</sub> value in the range of 1 to 10,000 nM.

Accordingly, the present invention includes a pharmaceutical composition which comprises a therapeutically effective amount of the compound of formula (I), a salt, hydrate, solvate or isomer thereof as an active ingredient and a pharmaceutically acceptable carrier; therefore, the pharmaceutical composition of the present invention exerts superior preventive and treating effects on GSK- $\beta$ -dependent diseases such as fatness, diabetes and dementia and the like.

A pharmaceutical formulation may be prepared in accordance with any of the conventional procedures. In preparing the formulation, the active ingredient is preferably admixed or diluted with a carrier, or enclosed within a carrier, sachet or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material acting as a vehicle, excipient or medium for the active ingredient. Thus, the formulations may be in the form of a tablet, pill, powder, sachet, elixir, suspension, emulsion, solution, syrup, aerosol, soft and hard gelatin capsule, sterile injectable solution, sterile packaged powder and the like.

Examples of suitable carriers, excipients, and diluents are lactose, dextrose, sucrose, sorbitol, mannitol, calcium silicate, cellulose, methyl cellulose, microcrystalline cellulose, polyvinylpyrrolidone, water, methylhydroxybenzoates, propylhydroxybenzoates, talc, magnesium stearate and mineral oil. The formulations may additionally include fillers, antiagglutinating agents, lubricating agents, wetting agents, flavoring agents, emulsifiers, preservatives and the like. The compositions of the invention may be formulated so as to provide quick, sustained or delayed release of the active ingredient after their administration to a mammal by employing any of the procedures well known in the art.

The pharmaceutical composition of the present invention can be administered via various routes including oral, transdermal, subcutaneous, intravenous and intramuscular introduction. In case of human, a typical daily dose of the compound of formula (I) may range from about 0.01 to 100 mg/kg body weight, preferably 0.1 to 50 mg/kg body weight, and can be administered in a single dose or in divided doses. However, it should be understood that the amount of the active ingredient actually administered ought to be determined in light of various relevant factors including the condition to be treated, the chosen route of administration, the age, sex and body weight of the individual patient, and the severity of the patient's symptom; and, therefore, the above dose should not be intended to limit the scope of the invention in any way.

The following examples are intended to further illustrate the present invention without limiting its scope.

<u>Preparation Example 1</u>: Preparation of Wang resin (p-benzyloxybenzyl alcohol resin)-supported 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid ( $R^1 = H, R^2 = H$  and  $R^3 = H$ )

20

5

10

(1) Preparation of 3-amino-4-methoxy benzoic acid methyl ester

3-amino-4-methoxy benzoic acid (40 g, 0.239 mol) was dissolved in methanol,  $H_2SO_4$  (38.14 ml, 0.717 mol) was added dropwise thereto and refluxed for 12 hours. The resulting mixture was cooled to room temperature and concentrated under a reduced pressure to remove methanol, neutralized with NaHCO<sub>3</sub>, extracted with ethyl acetate, and the extract was concentrated under a reduced pressure. The resulting residue was purified by recrystallization from ethyl acetate/hexane to obtain the title compound (39 g, 0.215 mol) in a yield of 90 %.

30

25

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.87-7.78 (2H, m), 7.22 (1H, d), 3.93 (3H, s), 3.82 (3H, s)

MW: 181

10

15

25

30

(2) Preparation of 4-methoxy-3-[(N-chloro-benzimidoyl)-amino]-benzoic acid methyl ester

Anhydrous p-toluene sulfonic acid (41.99 g, 220.8 mmol) was melted at 120 °C and 3-amino-4-methoxy benzoic acid methyl ester (20 g, 110.38 mmol) obtained in step 1 and benzonitrile (22.77 g, 220.8 mmol) were added thereto and stirred at 180 °C for 5 hours. The resulting solution was cooled to room temperature and the reaction was stopped by adding NaHCO<sub>3</sub> thereto. The resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The concentrate was dissolved in 50% methanol and 5% NaOCl (56 ml, 37.65 mmol) was added dropwise thereto. After 5 min, the resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chlomatography (eluent – MeOH/CDCl<sub>3</sub> = 5:95, Merck, Silicagel 60) to obtain the title compound (31 g, 25.10 mmol) in a yield of 88%.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.78 (1H, d), 7.48(1H, s), 7.37-7.24 (5H, m), 20 6.95 (1H, d), 3.78 (6H, s) MW: 318

(3) Preparation of 7-methoxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid methyl ester

4-methoxy-3-[(N-chloro-benzimidoyl)-amino]-benzoic acid methyl ester (8 g, 25.10 mmol) obtained in step 1 was dissolved in 50 ml of 50% methanol and NaHCO<sub>3</sub> (5.32 g, 50.20 mmol) was added dropwise thereto at room temperature and refluxed for 5 min. The resulting solution was cooled to room temperature, extracted with ethyl acetate, and the extract was concentrated under a reduced pressure. The resulting residue was purified by recrystallization from ethyl acetate/hexane to obtain the title compound (6 g, 15.94 mmol) in a yield of 86 %.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 10.65 (1H, br), 8.23 (2H, d), 7.49 (3H, m), 6.75 (1H, d), 4.13 (3H, s), 3.99 (3H, s) MW : 282

(4) Preparation of 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid

7-methoxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid methyl ester (4.5 g, 15.94 mmol) obtained in step 3 was dissolved in 100 ml of toluene, aluminum chloride (9.56 g, 71.73 mmol) was added thereto and refluxed for 8 hours. The resulting solution was cooled to room temperature, the reaction was stopped by adding 3 N HCl thereto and stirred for 30 min. The precipitate formed was filtered, washed with benzene and dried to obtain the title compound (3.5 g, 13.77 mmol) in a yield of 86%.

 $^{1}$ H NMR (DMSO- $d_{6}$ ): δ 8.29 (2H, d), 7.68 (1H, d), 7.56-7.49 (3H, m), 6.67 (1H, d) MW : 254

15

10

5

(5) Preparation of 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid methyl ester

7-methoxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid (2.00 g, 7.46 mmol) obtained in step 4 was dissolved in 30 ml of methanol, H<sub>2</sub>SO<sub>4</sub> (2.00 ml, 37.28 mmol) was added dropwise thereto and refluxed for 15 hours. The resulting solution was cooled to room temperature, concentrated under a reduced pressure to remove methanol, and the residue was neutralized with NaHCO<sub>3</sub>. Then, the neutralized residue was extracted with ethyl acetate and concentrated under a reduced pressure to obtain a residue which purified by recrystallization from CHCl<sub>3</sub>/MeOH/hexane to obtain the title compound (1.7 g, 5.89 mmol) in a yield of 83 %.

<sup>1</sup>H NMR (CH<sub>3</sub>OH-d<sub>4</sub>): δ 7.82 (1H, d), 7.42-7.25 (5H, m), 6.64 (1H, 30 d), 4.92 (3H, s)
MW : 268

(6) Preparation of Wang resin (p-benzyloxybenzyl alcohol resin)-supported 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid methyl ester

35

p-nitrophenyl carbonate Wang resin (476 mg, 0.67 mmol) was dissolved in DMF, and 7-hydroxy-2-phenyl-1H-benzoimidazole-4-

carboxylic acid methyl ester (567 mg, 2.01 mmol) obtained in step 5,  $Cs_2CO_3$  (655 mg, 2.01 mmol) and KI (334 mg, 2.01 mmol) were added thereto to be stirred at 50 to 60  $^{\circ}$ C for 12 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with DMF, MeOH and  $CH_2Cl_2$  and dried to obtain the title compound (608 mg, 0.65 mmol) in a yield of 98 %.

(7) Preparation of Wang resin-supported 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid methyl ester

10

15

5

Wang resin-supported 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid methyl ester (570 mg, 0.47 mmol) obtained in step 6 was dissolved in THF, LiOH·H<sub>2</sub>O (99 mg, 2.35 mmol) in MeOH-H<sub>2</sub>O (2:1) was added thereto and refluxed for 5 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with MeOH and CH<sub>2</sub>Cl<sub>2</sub>, and dried to obtain the title compound (551 mg, 0.42 mmol) in a yield of 90 %.

Preparation Example 2: Preparation of 2-(4-chloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid ( $R^1 = H$ ,  $R^2 = H$  and  $R^3 = Cl$ )

- (1) Preparation of 3-[(4-chloro-N-chloro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester
- Anhydrous p-toluene sulfonic acid (41.99 g, 220.76 mmol) was 25 melted at 120 °C and 3-amino-4-methoxy benzoic acid methyl ester (20 g, 110.38 mmol) obtained in step 1 of Preparation Example 1 and 4chlorobenzonitrile (22.78 g, 165.57 mol) were added thereto and stirred at 160 °C for 8 hours. The resulting solution was cooled to room temperature and the reaction was stopped by adding 1M NaHCO<sub>3</sub> thereto. 30 The resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The concentrate was dissolved in 500 ml of 50% methanol and 5% NaOCl (197 ml, 132.46 mmol) was added dropwise thereto. After 5 min, the resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and 35 concentrated under a reduced pressure. The resulting residue was purified by silica gel column chlomatography (eluent - MeOH: CDCl<sub>3</sub> = 5:95,

30

Merck, Silicagel 60) to obtain the title compound (19.43 g, 55.19 mmol) in a yield of 50%.

<sup>1</sup>H NMR (CH<sub>3</sub>OH-d<sub>4</sub>): δ 7.62 (2H, m), 7.22-7.15 (4H, m), 6.59 5 (1H, s), 4.00-3.80 (6H, d) MW: 352

(2) Preparation of 2-(4-chloro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester

3-[(4-chloro-N-chloro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester (5.5 g, 15.63 mmol) obtained in step 1 was dissolved in 40 ml of 50% methanol and Na<sub>2</sub>CO<sub>3</sub> (3.53 g, 33.26 mmol) was added dropwise thereto at room temperature and refluxed for 5 min. The resulting solution was cooled to room temperature, extracted with ethyl acetate, the extract was concentrated under a reduced pressure. The resulting residue was purified

by silica gel column chromatography to obtain the title compound (2.57 g,

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.15 (2H, d), 7.95 (1H, d), 7.51 (2H, m), 6.75 (1H, d), 4.06 (3H, s)

8.13 mmol) in a yield of 52 %.

MW:316

(3) Preparation of 2-(4-chloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-25 carboxylic acid

2-(4-chloro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester (1.0 g, 3.16 mmol) obtained in step 2 was dissolved in 10 ml of toluene, aluminum chloride (2.11 g, 15.8 mmol) was added thereto and refluxed for 8 hours. The resulting solution was cooled to room temperature, the reaction was stopped by adding 3 N HCl thereto and stirred for 30 min. The precipitate formed was filtered, washed with benzene and dried to obtain the title compound (745 mg, 2.59 mmol) in a yield of 82%.

<sup>1</sup>H NMR (CH<sub>3</sub>OH- $d_4$ ): δ 8.06 (3H, m), 7.50 (2H, m), 6.97 (1H, d) MW : 288

25

30

(4) Preparation of 2-(4-chloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester

2-(4-chloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid
(200 mg, 0.69 mmol) obtained in step 3 was dissolved in 5 ml of methanol,
H<sub>2</sub>SO<sub>4</sub> (0.18 ml, 3.45 mmol) was added dropwise thereto and refluxed for 15
hours. The resulting solution was cooled to room temperature,
concentrated under a reduced pressure to remove methanol, and the residue
was neutralized with 1M NaHCO<sub>3</sub>. Then, the neutralized residue was
extracted with ethyl acetate and concentrated under a reduced pressure to
obtain a residue which was purified by silica gel column chromatography
(eluent – MeOH / CDCl<sub>3</sub> = 5 / 95, Merck, Silicagel 60) to obtain the title
compound (166 mg, 0.55 mmol) in a yield of 80 %.

<sup>1</sup>H NMR (CH<sub>3</sub>OH- $d_4$ ): δ 10.75 (1H, Br), 7.89 (3H, m), 7.46 (2H, d), 6.82 (1H, d), 3.39 (3H, s) MW : 302

(5) Preparation of Wang resin-supported 2-(4-chloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester

(4-bromomethylphenoxy)-methyl polystyrene Wang resin (476 mg, 0.67 mmol) was dissolved in 5 ml of DMF, and 2-(4-chloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester (567 mg, 2.01 mmol) obtained in step 4, Cs<sub>2</sub>CO<sub>3</sub> (655 mg, 2.01 mmol) and KI (334 mg, 2.01 mmol) were added thereto to be stirred at 50 to 60 ℃ for 12 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with DMF, MeOH and CH<sub>2</sub>Cl<sub>2</sub> and dried to obtain the title compound (608 mg, 0.65 mmol) in a yield of 98 %.

(6) Preparation of Wang resin-supported 2-(4-chloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid

Wang resin-supported 2-(4-chloro-phenyl)-7-hydroxy-1H-35 benzoimidazole-4-carboxylic acid methyl ester (570 mg, 0.47 mmol) obtained in step 5 was dissolved in THF, LiOH H<sub>2</sub>O (99 mg, 2.35 mmol) in MeOH-H<sub>2</sub>O (1:1) was added thereto and the resulting mixture was refluxed for 5 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with MeOH and CH<sub>2</sub>Cl<sub>2</sub>, and dried to obtain the title compound (551 mg, 0.42 mmol) in a yield of 90 %.

- 5 <u>Preparation Example 3</u>: Preparation of 2-(2,4-dichloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid ( $R^1 = Cl$ ,  $R^2 = H$  and  $R^3 = Cl$ )
  - (1) Preparation of 3-[(2,4-dichloro-N-chloro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester

10

15

20

Anhydrous p-toluene sulfonic acid (20.99 g, 110.04 mmol) was melted at 120 °C and 3-amino-4-methoxy benzoic acid methyl ester (10 g, 55.20 mmol) obtained in step 1 of Preparation Example 1 and 2,4-dichlorobenzonitrile (18.99 g, 110.04 mol) were added thereto and stirred at 180 °C for 6 hours. The resulting solution was cooled to room temperature and the reaction was stopped by adding NaHCO<sub>3</sub> thereto. The resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The concentrate was dissolved in 50% methanol and 5% NaOCl (30 m $\ell$ , 20.64 mmol) was added dropwise thereto. After 5 min, the resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent – MeOH: CDCl<sub>3</sub> = 5:95, Merck, Silicagel 60) to obtain the title compound (18 g, 10.32 mmol) in a yield of 84%.

25

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.23 (1H, br), 7.75 (1H, d), 7.44 (1H, d), 7.36-7.26 (2H, m), 7.03 (1H, s), 6.88 (1H, d), 3.96 (3H, s), 3.76 (3H, s) MW : 318

- 30 (2) Preparation of 2-(2,4-dichloro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester
- 3-[(2,4-dichloro-*N*-chloro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester (4 g, 10.32 mmol) obtained in step 1 was dissolved in 50 ml of 50% methanol and NaHCO<sub>3</sub> (2.19 g, 20.64 mmol) was added dropwise thereto at room temperature and refluxed for 5 min. The resulting solution was cooled to room temperature, extracted with ethyl acetate, and the extract

30

35

was concentrated under a reduced pressure. The resulting residue was purified by recrystallization from ethyl acetate/hexane to obtain the title compound (3.2 g, 5.47 mmol) in a yield of 88 %.

- <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.54 (1H, d), 7.94 (1H, d), 7.48 (1H, s), 7.42 (1H, d), 6.76 (1H,d), 4.44 (3H, s), 3.99 (3H, s)

  MW: 351
- (3) Preparation of 2-(2,4-dichloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-10 carboxylic acid
  - 2-(2,4-dichloro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester (1.9 g, 5.47 mmol) obtained in step 2 was dissolved in 100 ml of toluene, aluminum chloride (3.61 g, 27.05 mmol) was added thereto and refluxed for 8 hours. The resulting solution was cooled to room temperature, the reaction was stopped by adding 3 N HCl thereto and stirred for 30 min. The precipitate formed was filtered, washed with benzene and dried to obtain the title compound (1.63 g, 5.03 mmol) in a yield of 92%.
- <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 8.19 (1H, d), 7.78 (1H, d), 7.62-7.55 (2H, m), 6.82 (1H, d)

  MW: 323
- (4) Preparation of 2-(2,4-dichloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-25 carboxylic acid methyl ester
  - 2-(2,4-dichloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid (1.63 g, 5.03 mmol) obtained in step 3 was dissolved in 30 ml of methanol, and H<sub>2</sub>SO<sub>4</sub> (1.08 ml, 20.12 mmol) was added dropwise thereto and refluxed for 15 hours. The resulting solution was cooled to room temperature, concentrated under a reduced pressure to remove methanol, and the residue was neutralized with NaHCO<sub>3</sub>. Then, the neutralized residue was extracted with ethyl acetate and concentrated under a reduced pressure to obtain a residue which was purified by recrystallization from ethyl acetate/hexane to obtain the title compound (1.5 g, 3.62 mmol) in a yield of 86 %.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 11.42 (1H, br), 8.21 (1H, d), 7.89 (1H, d), 7.56 (1H, s), 7.38 (1H, d), 6.82 (1H, d), 3.99 (3H, s) MW: 337

5 (5) Preparation of Wang resin-supported 2-(2,4-chloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester

p-nitrophenyl carbonate Wang resin (476 mg, 0.67 mmol) was dissolved in DMF, and 2-(2,4-dichloro-phenyl)-7-hydroxy-1Hbenzoimidazole-4-carboxylic acid methyl ester (567 mg, 2.01 mmol), obtained in step 4, Cs<sub>2</sub>CO<sub>3</sub> (655 mg, 2.01 mmol) and KI (334 mg, 2.01 mmol) were added thereto to be stirred at 50 to 60 °C for 12 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with DMF, MeOH and CH<sub>2</sub>Cl<sub>2</sub> and dried to obtain the title compound (608 mg, 0.65 mmol) in a yield of 98 %.

- (6) Preparation of Wang resin-supported 2-(2,4-dichloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid
- Wang resin-supported 2-(2,4-dichloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester (570 mg, 0.47 mmol) obtained in step 5 was dissolved in THF, LiOH H<sub>2</sub>O (99 mg, 2.35 mmol) in MeOH-H<sub>2</sub>O (2:1) was added thereto and the resulting mixture was refluxed for 5 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with MeOH and CH<sub>2</sub>Cl<sub>2</sub>, and dried to obtain the title compound (551 mg, 0.42 mmol) in a yield of 90 %.

<u>Preparation Example 4</u>: Preparation of Wang resin-supported 2-(4-fluorophenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid ( $R^1 = H$ ,  $R^2 = H$  and  $R^3 = F$ )

- (1) Preparation of 3-[(4-fluoro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester
- Anhydrous p-toluene sulfonic acid (41.99 g, 220.76 mmol) was melted at 120 °C and 3-amino-4-methoxy benzoic acid methyl ester (20 g, 110.38 mmol) obtained in step 1 of Preparation Example 1 and 4-

fluorobenzonitrile (20.00 g, 165.57 mol) were added thereto and stirred at  $160\,^{\circ}$ C for 8 hours. The resulting solution was cooled to room temperature and the reaction was stopped by adding NaHCO<sub>3</sub> thereto. The resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent – MeOH: CDCl<sub>3</sub> = 5:95, Merck, Silicagel 60) to obtain the title compound (22.67 g, 75.06 mmol) in a yield of 68%.

- <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.92-7.75 (4H, m), 7.15-7.02 (3H, m), 3.87-3.81 (6H, d)
  MW: 302
- (2) Preparation of 2-(4-fluoro-phenyl)-7-methoxy-1H-benzoimidazole-4-15 carboxylic acid methyl ester

3-[(4-fluoro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester (10 g, 34.48 mmol) obtained in step 1 was dissolved in 50% methanol and 5% NaOCl (61 ml, 41.38 mmol) was added dropwise thereto at room temperature. After 5 min, Na<sub>2</sub>CO<sub>3</sub> (7.31 g, 68.96 mmol) was added dropwise thereto and refluxed for 5 min. The resulting solution was cooled to room temperature, extracted with ethyl acetate, and the extract was concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (5.66 g, 19.65 mmol) in a yield of 57 %.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.18 (2H, t), 7.91 (1H, d), 7.30-7.25 (2H, t), 6.65 (1H, d), 6.85 (1H, d), 4.08 (3H, s), 3.98 (3H, s)
MW: 300

30

20

25

- (3) Preparation of 2-(4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid
- 2-(4-fluoro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic 35 acid methyl ester (3 g, 10.00 mmol) obtained in step 2 was dissolved in toluene, aluminum chloride (6.67 g, 30.00 mmol) was added thereto and refluxed for 8 hours. The resulting solution was cooled to room

temperature, the reaction was stopped by adding 3 N HCl thereto and stirred for 30 min. The precipitate formed was filtered, washed with benzene and dried to obtain the title compound (1.96 g, 7.20 mmol) in a yield of 72%.

<sup>5</sup> H NMR (MeOH-d<sub>4</sub>): δ 8.19-8.15 (2H, t), 8.06 (1H, d), 7.50-7.44 (2H, t), 7.00 (1H, d) MW: 272

(4) Preparation of 2-(4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-10 carboxylic acid methyl ester

2-(4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid (500 mg, 1.84 mmol) obtained in step 3 was dissolved in methanol, H<sub>2</sub>SO<sub>4</sub> (0.49 ml, 9.20 mmol) was added dropwise thereto and refluxed for 15 hours.

The resulting solution was cooled to room temperature, concentrated under a reduced pressure to remove methanol, and the residue was neutralized with NaHCO<sub>3</sub>. Then, the neutralized residue was extracted with ethyl acetate and concentrated under a reduced pressure to obtain a residue which was purified by silica gel chromatography to obtain the title compound (397 mg, 1.39 mmol) in a yield of 76 %.

<sup>1</sup>H NMR (CH<sub>3</sub>OH-d<sub>4</sub>): δ 8.22-8.18 (2H, t), 7.80 (1H, d), 7.32-7.26 (2H, t), 6.70 (1H, d), 3.97 (3H, s) MW : 286

25

(5) Preparation of Wang resin-supported 2-(4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester

(4-bromomethylphenoxy)-methyl polystyrene Wang resin (476 mg, 0.67 mmol) was dissolved in DMF, and 2-(4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester (567 mg, 2.01 mmol) obtained in step 4, Cs<sub>2</sub>CO<sub>3</sub> (655 mg, 2.01 mmol) and KI (334 mg, 2.01 mmol) were added thereto to be stirred at 50 to 60 ℃ for 12 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with DMF, MeOH and CH<sub>2</sub>Cl<sub>2</sub> and dried to obtain the title compound (608 mg, 0.65 mmol) in a yield of 98 %.

(6) Preparation of Wang resin-supported 2-(4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid

Wang resin-supported 2-(4-fluoro-phenyl)-7-hydroxy-1H-5 benzoimidazole-4-carboxylic acid methyl ester (570 mg, 0.47 mmol) obtained in step 5 was dissolved in THF, LiOH·H<sub>2</sub>O (99 mg, 2.35 mmol) in MeOH-H<sub>2</sub>O (2:1) was added thereto and the resulting mixture was refluxed for 5 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with MeOH and CH<sub>2</sub>Cl<sub>2</sub>, and dried to obtain the title compound (551 mg, 0.42 mmol) in a yield of 90 %.

<u>Preparation Example 5</u>: Preparation of Wang resin-supported 2-(2,4-difluorophenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid ( $R^1 = F, R^2 = H$  and  $R^3 = F$ )

(1) Preparation of 3-[(2,4-difluoro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester

Anhydrous p-toluene sulfonic acid (25.0 g, 137.43 mmol) was melted at 120 °C and 3-amino-4-methoxy benzoic acid methyl ester (10 g, 55.25 mmol) obtained in step 1 of Preparation Example 1 and 2,4-difluorobenzonitrile (11.53 g, 82.87 mol) were added thereto and stirred at 160 °C for 8 hours. The resulting solution was cooled to room temperature and the reaction was stopped by adding NaHCO<sub>3</sub> thereto. The resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (10.0 g, 31.22 mmol) in a yield of 57%.

- <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.31-8.22 (1H, m), 7.82-7.79 (1H, d), 7.65 (1H, s), 7.02-6.85 (3H, m), 3.88 (6H, s) MW: 320
- (2) Preparation of 2-(2,4-difluoro-phenyl)-7-methoxy-1H-benzoimidazole-4-35 carboxylic acid methyl ester

20

methyl ester (9.5 g, 29.66 mmol) obtained in step 1 was dissolved in 50% methanol and 5% NaOCl (53 ml, 35.71 mmol) was added dropwise thereto at room temperature. After 5 min, Na<sub>2</sub>CO<sub>3</sub> (6.29 g, 59.34 mmol) was added dropwise thereto and refluxed for 5 min. The resulting solution was cooled to room temperature, extracted with ethyl acetate, and the extract was concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (3.50 g, 11.0 mmol) in a yield of 37 %.

- <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 10.99 (1H, bs). 8.65-8.57 (1H, m), .92 (1H, d), 7.10-6.97 (2H, m), 6.76 (1H, d), 4.13 (3H, s), 4.00 (3H, s) MW : 318
- (3) Preparation of 2-(2,4-difluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4carboxylic acid
  - 2-(2,4-difluoro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester (2.24 g, 7.04 mmol) obtained in step 2 was dissolved in toluene, aluminum chloride (3.75 g, 28.12 mmol) was added thereto and refluxed for 8 hours. The resulting solution was cooled to room temperature, the reaction was stopped by adding 3 N HCl thereto and stirred for 30 min. The precipitate formed was filtered, washed with benzene and dried to obtain the title compound (1.70 g, 5.86 mmol) in a yield of 83%.
- <sup>1</sup>H NMR (CH<sub>3</sub>OH- $d_4$ ): δ 8.13-8.03 (2H, m), 7.47-7.33 (2H, m), 7.04 (1H, d) MW : 290
- (4) Preparation of 2-(2,4-difluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-30 carboxylic acid methyl ester
- 2-(2,4-difluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid (1.70 mg, 5.86 mmol) obtained in step 3 was dissolved in methanol, SOCl<sub>2</sub> (8.2 ml, 112 mmol) was added dropwise thereto and refluxed for 15 hours. The resulting solution was cooled to room temperature, concentrated under a reduced pressure to remove methanol, and the residue was neutralized with NaHCO<sub>3</sub>. Then, the neutralized residue was extracted

with ethyl acetate and concentrated under a reduced pressure to obtain a residue which was purified by silica gel chromatography to obtain the title compound (1.50 mg, 1.64 mmol) in a yield of 84 %.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 12.04 (1H, bs), .30-8.04 (1H, m), 7.73 (1H, d), 7.55-7.48 (1H, m), 7.33-7.27 (1H, m), 6.70 (1H, d), 4.01 (3H, s) MW : 304

(5) Preparation of Wang resin-supported 2-(2,4-difluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester

(4-bromomethylphenoxy)-methyl polystyrene Wang resin (476 mg, 0.67 mmol) was dissolved in DMF, and 2-(2,4-difluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester (567 mg, 2.01 mmol) obtained in step 4,  $Cs_2CO_3$  (655 mg, 2.01 mmol) and KI (334 mg, 2.01 mmol) were added thereto to be stirred at 50 to 60 °C for 12 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with DMF, MeOH and  $CH_2Cl_2$  and dried to obtain the title compound (608 mg, 0.65 mmol) in a yield of 98 %.

20

10

15

(6) Preparation of Wang resin-supported 2-(2,4-difluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid

Wang resin-supported 2-(2,4-difluoro-phenyl)-7-hydroxy-1H25 benzoimidazole-4-carboxylic acid methyl ester (570 mg, 0.47 mmol)
obtained in step 5 was dissolved in THF, LiOH:H<sub>2</sub>O (99 mg, 2.35 mmol) in
MeOH-H<sub>2</sub>O was added thereto and the resulting mixture was refluxed for 5
hours. The resulting solution was cooled to room temperature and filtered.
The filtrate was washed with MeOH and CH<sub>2</sub>Cl<sub>2</sub>, and dried to obtain the title
compound (551 mg, 0.42 mmol) in a yield of 90 %.

<u>Preparation Example 6</u>: Preparation of Wang resin-supported 2-(2-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid ( $R^1 = Cl$ ,  $R^2 = H$  and  $R^3 = F$ )

35

(1) Preparation of 3-[(2-chloro-4-fluoro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester

10

Anhydrous *p*-toluene sulfonic acid (41.99 g, 220.76 mmol) was melted at 120 °C and 3-amino-4-methoxy benzoic acid methyl ester (20 g, 110.38 mmol) obtained in step 1 of Preparation Example 1 and 2-chloro-4-fluorobenzonitrile (25.76 g, 165.57 mol) were added thereto and stirred at 160 °C for 8 hours. The resulting solution was cooled to room temperature and the reaction was stopped by adding NaHCO<sub>3</sub> thereto. The resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (26.70 g, 79.47 mmol) in a yield of 72%.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.92-7.75 (4H, m), 7.15-7.02 (3H, m), 3.87-3.81 (6H, d)

- 15 MW: 336
  - (2) Preparation of 2-(2-chloro-4-fluoro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester
- 3-[(2-chloro-4-fluoro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester (10 g, 29.76 mmol) obtained in step 1 was dissolved in 50% methanol and 5% NaOCl (53 ml, 35.71 mmol) was added dropwise thereto at room temperature. After 5 min, Na<sub>2</sub>CO<sub>3</sub> (6.31 g, 59.52 mmol) was added dropwise thereto and refluxed for 5 min. The resulting solution was cooled to room temperature, extracted with ethyl acetate, the extract was concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (5.17 g, 15.48 mmol) in a yield of 52 %.
- <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.18 (2H, t), .91 (1H, d), 7.30-7.25 (2H, t), 6.65 (1H, d), 6.85 (1H, d), 4.08 (3H, s), 3.98 (3H, s) MW : 334
- (3) Preparation of 2-(2-chloro-4-fluoro-phenyl)-7-hydroxy-1H-35 benzoimidazole-4-carboxylic acid
  - 2-(2-chloro-4-fluoro-phenyl)-7-methoxy-1H-benzoimidazole-4-

10

35

carboxylic acid methyl ester (3 g, 8.98 mmol) obtained in step 2 was dissolved in toluene and aluminum chloride (5.99 g, 44.90 mmol) was added thereto, refluxed for 8 hours. The resulting solution was cooled to room temperature, the reaction was stopped by adding 3 N HCl thereto and stirred for 30 min. The precipitate formed was filtered, washed with benzene and dried to obtain the title compound (1.87 g, 6.11 mmol) in a yield of 68%.

<sup>1</sup>H NMR (CH<sub>3</sub>OH-d<sub>4</sub>): δ 8.19-8.15 (2H, t), 8.06 (1H, d), 7.50-7.44 (2H, t), 7.00 (1H, d) MW: 306

- (4) Preparation of 2-(2-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester
- 2-(2-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid (500 mg, 1.63 mmol) obtained in step 3 was dissolved in methanol, H<sub>2</sub>SO<sub>4</sub> (0.43 ml, 8.15 mmol) was added dropwise thereto and refluxed for 15 hours. The resulting solution was cooled to room temperature, concentrated under a reduced pressure to remove methanol, and the residue was neutralized with NaHCO<sub>3</sub>. Then, the neutralized residue was extracted with ethyl acetate and concentrated under a reduced pressure to obtain a residue which was purified by silica gel chromatography to obtain the title compound (393 mg, 1.23 mmol) in a yield of 67 %.
- <sup>1</sup>H NMR (CH<sub>3</sub>OH-d<sub>4</sub>): δ 8.22-8.18 (2H, t), 7.80 (1H, d), 7.32-7.26 (2H, t), 6.70 (1H, d), 3.97 (3H, s) MW: 320
- (5) Preparation of Wang resin-supported 2-(2-chloro-4-fluoro-phenyl)-7 30 hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester
  - (4-bromomethylphenoxy)-methyl polystyrene Wang resin (476 mg, 0.67 mmol) was dissolved in DMF, and 2-(2-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester (567 mg, 2.01 mmol) obtained in step 4,  $Cs_2CO_3$  (655 mg, 2.01 mmol) and KI (334 mg, 2.01 mmol) were added thereto to be stirred at 50 to 60 °C for 12 hours. The resulting solution was cooled to room temperature and filtered. The

30

35

filtrate was washed with DMF, MeOH and CH<sub>2</sub>Cl<sub>2</sub> and dried to obtain the title compound (608 mg, 0.65 mmol) in a yield of 98 %.

(6) Preparation of Wang resin-supported 2-(2-chloro-4-fluoro-phenyl)-7-5 hydroxy-1H-benzoimidazole-4-carboxylic acid

Wang resin-supported 2-(2-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester (570 mg, 0.47 mmol) obtained in step 5 was dissolved in THF, LiOH H<sub>2</sub>O (99 mg, 2.35 mmol) in MeOH-H<sub>2</sub>O was added thereto and the resulting mixture was refluxed for 5 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with MeOH and CH<sub>2</sub>Cl<sub>2</sub>, and dried to obtain the title compound (551 mg, 0.42 mmol) in a yield of 90 %.

- Preparation Example 7: Preparation of Wang resin-supported 2-(3-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid ( $R^1 = H, R^2 = Cl$  and  $R^3 = F$ )
- (1) Preparation of 3-[(3-chloro-4-fluoro-benzimidoyl)-amino]-4-methoxy-20 benzoic acid methyl ester

Anhydrous *p*-toluene sulfonic acid (10 g, 52.57 mmol) was melted at 120 °C and 3-amino-4-methoxy benzoic acid methyl ester (3.88 g, 21.44 mmol) obtained in step 1 of Preparation Example 1 and 3-chloro-4-fluorobenzonitrile (5.0 g, 32.14 mol) were added thereto and stirred at 160 °C for 8 hours. The resulting solution was cooled to room temperature and the reaction was stopped by adding NaHCO<sub>3</sub> thereto. The resulting mixture was extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (3.24 g, 9.62 mmol) in a yield of 45%.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.96-7.95 (1H, m), 7.76-7.73 (2H, m), 7.60 (1H, bs), 7.17-7.11 (1H, m), 6.93(1H, d), 3.85(3H, s), 3.84 (3H, d) MW: 336

10

25

(2) Preparation of 2-(3-chloro-4-fluoro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester

3-[(3-chloro-4-fluoro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester (3.24 g, 9.62 mmol) was dissolved in 50% methanol and 5% NaOCl (18 ml, 11.90 mmol) was added dropwise thereto at room temperature. After 5 min, Na<sub>2</sub>CO<sub>3</sub> (2.04 g, 19.25 mmol) was added dropwise thereto and refluxed for 5 min. The resulting solution was cooled to room temperature, extracted with ethyl acetate, and the extract was concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (0.95 g, 2.83 mmol) in a yield of 30 %.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 10.68 (1H, bs), 8.23-8.20 (1H, m), 7.96-7.91 (1H, m), 7.87 (1H, d), 7.27-7.20 (1H, m), 6.73 (1H, d), 4.10 (3H, s), 3.97 (3H, s)

MW: 334

- (3) Preparation of 2-(3-chloro-4-fluoro-phenyl)-7-hydroxy-1H-20 benzoimidazole-4-carboxylic acid
  - 2-(3-chloro-4-fluoro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester (0.95 g, 8.98 mmol) obtained in step 2 was dissolved in toluene, aluminum chloride (1.5 g, 11.25 mmol) was added thereto and refluxed for 8 hours. The resulting solution was cooled to room temperature, the reaction was stopped by adding 3 N HCl thereto and stirred for 30 min. The precipitate formed was filtered, washed with benzene and dried to obtain the title compound (0.81 g, 2.64 mmol) in a yield of 80%.
- <sup>1</sup>H NMR (MeOH-d<sub>4</sub>): δ 8.34 (1H, dd), 8.22-8.08 (2H, m), 7.62 (1H, t), 7.03 (1H, d)
  MW: 306
- (4) Preparation of 2-(3-chloro-4-fluoro-phenyl)-7-hydroxy-1H-35 benzoimidazole-4-carboxylic acid methyl ester
  - 2-(3-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-

carboxylic acid (800 mg, 2.64 mmol) obtained in step 3 was dissolved in methanol, SOCl<sub>2</sub> (1.93 ml, 26.41 mmol) was added dropwise thereto and refluxed for 15 hours. The resulting solution was cooled to room temperature, concentrated under a reduced pressure to remove methanol, and the residue was neutralized with NaHCO<sub>3</sub>. Then, the neutralized residue was extracted with ethyl acetate and concentrated under a reduced pressure to obtain a residue which was purified by silica gel chromatography to obtain the title compound (690 mg, 2.15 mmol) in a yield of 81 %.

- <sup>1</sup>H NMR (DMSO- $d_6$ ): δ 12.39 (1H, bs), 8.56 (1H, d), 8.30 (1H, bs), 7.72 (1H, d), 7.59 (1H, t), 6.69 (1H, d), 3.90 (3H, s) MW : 320
- (5) Preparation of Wang resin-supported 2-(3-chloro-4-fluoro-phenyl)-7-15 hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester

(4-bromomethylphenoxy)-methyl polystyrene Wang resin (476 mg, 0.67 mmol) was dissolved in DMF, and 2-(3-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid methyl ester (567 mg, 2.01 mmol) obtained in step 4, Cs<sub>2</sub>CO<sub>3</sub> (655 mg, 2.01 mmol) and KI (334 mg, 2.01 mmol) were added thereto to be stirred at 50 to 60 ℃ for 12 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with DMF, MeOH and CH<sub>2</sub>Cl<sub>2</sub> and dried to obtain the title compound (608 mg, 0.65 mmol) in a yield of 98 %.

25

- (6) Preparation of Wang resin-supported 2-(3-chloro-4-fluoro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid
- Wang resin-supported 2-(3-chloro-4-fluoro-phenyl)-7-hydroxy-1H-30 benzoimidazole-4-carboxylic acid methyl ester (570 mg, 0.47 mmol) obtained in step 5 was dissolved in THF, LiOH:H<sub>2</sub>O (99 mg, 2.35 mmol) in MeOH-H<sub>2</sub>O was added thereto and the resulting mixture was refluxed for 5 hours. The resulting solution was cooled to room temperature and filtered. The filtrate was washed with MeOH and CH<sub>2</sub>Cl<sub>2</sub>, and dried to obtain the title compound (551 mg, 0.42 mmol) in a yield of 90 %.
  - Example 1: Preparation of 7-hydroxy-2-phenyl-1H-benzoimidazole-4-

5

10

15

20

25

carboxylic acid amide ( $R^4R^5NH_2 = NH_4Cl$ )

Wang resin-supported 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid (36 mg, 0.03 mmol) obtained in Preparation Example 1 was dissolved in 3 ml of DMF and aluminum chloride (5 mg, 0.09 mmol), EDCI (18 mg, 0.09 mmol), DMAP (11 mg, 0.09 mmol) and HOBt (12 mg, 0.09 mmol) were added thereto and the resulting mixture was stirred at room temperature. The resulting solution was filtered, the filtrate was washed with DMF, MeOH and CH<sub>2</sub>Cl<sub>2</sub> and dried to obtain Wang resin-supported 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid amide.

Then, 30 mg of Wang resin-supported 7-hydroxy-2-phenyl-1H-benzoimidazole-4-carboxylic acid amide was dissolved in 0.2 ml of CH<sub>2</sub>Cl<sub>2</sub>, 0.2 ml of trifluoroacetic acid was added thereto and stirred for 30 min. The resulting solution was filtered, the filtrate was washed with MeOH and CH<sub>2</sub>Cl<sub>2</sub> and dried to obtain the title compound in a yield of 90%.

<sup>1</sup>H NMR (CH<sub>3</sub>OH-d<sub>4</sub>): δ 8.15 (2H, d), 7.84 (1H, d), 7.78-7.56 (3H, m), 6.83 (1H, m) MW : 253

Example 2 to 203

The same was a law at 1 11 12 D

The same procedure as described in Example 1 was repeated using  $R^4R^5NH_2$  listed in Table 2 to obtain the compounds 2 to 203, respectively.

	1		Te	Table 2		
Com	Pre	Chemical compound	R <sup>4</sup> N(CH <sub>2</sub> ) <sub>n</sub> R <sup>5</sup>	ㅁ	<sup>1</sup> H NMR (CH <sub>3</sub> OH- <i>d</i> <sub>4</sub> )	MM
No.	Š.					
8		7-hydroxy-2-phenyl-1H-benz	aniline	0	8 8.10 (2H, d), 7.87 (1H, d), 7.85-7.60 (3H, m),	329
		oimidazole-4-carboxylic				
		acid-phenylamide			m), 6.89 (1H, d)	
က		7-hydroxy-2-phenyl-1H-	4-hydroxyanili	0	6 8.28-8.03 (3H, m), 7.98-7.82 (1H, d), 7.79-7.56	345
		benzoimidazole-4-carboxylic	ne			
		acid(4-hydroxy-phenyl)-amide				
4	H	7-hydroxy-2-phenyl-1H-	1,4-diaminoph	0	6 8.28-8.14 (2H, m), 8.03-7.91 (3H, m), 7.71-7.56	344
		benzoimidazole-4-carboxylic	enylene		(3H, m), 7.46-7.34 (2H, d), 6.89-6.76 (1H, d)	
		acid (4-amino-phenyl)-amide				
2	<del>, - 1</del>	7-hydroxy-2-phenyl-1H-	4-hydroxycycl	0	6 8.08 (2H, d), 7.82 (1H, d), 7.78-7.50 (3H, m), 6.88	351
		benzoimidazole-4-carboxylic	ohexylamine			
		acid(4-hydroxy-cyclohexyl)~a			2.30-1.90 (4H, m), 1.85-1.20 (4H, m)	
		mide				
9	<del></del>	7-hydroxy-2-phenyl-1H-	4-(hydroxymet	0	6 8.20 (2H, d), 7.92 (2H, d), 7.81-7.70 (1H, m),	359
	<del></del>	benzoimidazole-4-carboxylic	hyl)aniline			-
		acid(4-hydroxymethyl-phenyl)			(1H, m), 6.89 (1H, d), 4.65 (2H, s)	
		-amide				
•				1		

7		7-hydroxy-2-phenyl-1H-	4-(hydroxyeth	0	\$ 8.14 (2H, d), 7.98 (1H, d), 7.78-7.60 (5H, m),	373
		benzoimidazole-4-carboxylic	yl)aniline			
		acid[4-(2-hydroxy-ethyl)-phe			(1H, t), 3.02 (1H, t), 2.81 (1H, t)	
		nyl]-amide				
∞	<del></del>	7-hydroxy-2-phenyl-1H-	4-(aminoethyl)	0	8 8.27-8.16 (2H, m), 7.95 (1H, d), 7.78 (2H, d),	372
		benzoimidazole-4-carboxylic	aniline		7.66-7.54 (3H, m), 7.44 (2H, d), 6.86 (1H, d), 3.19	
		acid[4-(2-amino-ethyl)-pheny			(2H, t), 2.92 (2H, t)	
		1]-amide				
6		7-hydroxy-2-phenyl-1H-	N-[2-(4-amin	0	8 8.20-8.02 (3H, m), 8.00 (2H, d), 7.70-7.68 (5H,	526
		benzoimidazole-4-carboxylic	o-phenyl)-eth		m), 7.38 (2H, d), 7.16 (2H, d), 6.94 (1H, d), 3.10 (2H,	
		acid{4-[2-(toluene-4-sulfonyl	yl]-4-methylb		t), 2.73 (2H, t), 2.43 (3H, s)	
		amino)-ethyl]-phenyl}-amide	enzenesulfona			
			mide			
10		7-hydroxy-2-phenyl-1H-	N-[2-(4-amin (	0	8 8.13 (2H, d), 7.98 (1H, d), 7.75-7.53 (5H, m), 7.29	450
		bezoimidazole-4-carboxylic	o-phenyl)-eth		(2H, d), 6.91 (1H, d), 3.30 (2H, t), 2.82 (2H, t)	
		acid[4-(2-methanesulfonylami	yl]-4-methane			
		no-ethyl)-phenyl]-amide	sulfonamide			

	7-hydroxy-2-phenyl-1H-	2-[2-(4-amino	0	8 7.45 (2H, d), 6.98-6.84 (4H, m), 6.82 (2H, d).	502
	bezoimidazole-4-carboxylic	phenyl)-ethyl]		6.73-6.54 (4H, m), 6.30 (2H, d), 5.89 (1H, d), 2.91	
	acid {4-[2-(1,3-dioxo-1,3-	-isoindole-1,3		(2H, t), 2.00 (2H, t)	
	dihydro-isoindole-2-yl)-ethyl]	-dione			
ł	-phenyl}-amide				
	7-hydroxy-2-phenyl-1H-	thiophene-2-	0	8 8.15 (2H, d), 8.06 (1H, d), 7.80-7.55 (7H, m),	518
	benzoimidazole-4-carboxylic	sulfonic acid		7.23-7.10 (3H, m), 7.05 (1H, d), 3.16 (2H, t), 2.80	
	$ acid\{4-[2-(thiophene-2-sulfon)][2-(4-amino-p)] $	[2-(4-amino-p		(2H, t)	
	ylamino)-ethyl]-phenyl}-amid	henyl)-ethyl]-			
ŀ	υ	amide			
	7-hydroxy-2-phenyl-1H-	N-[2-(4-amin (	0	8 8.17 (2H, d), 8.03 (1H, d), 7.77-7.68 (5H, m), 7.27	464
	benzoimidazole-4-carboxylic	o-phenyl)-eth		(2H, d), 7.01 (1H, d), 3.31 (2H, t), 2.99 (2H, q), 2.85	
	acid[4-(2-ethanesulfonylamino	yl]-ethanesulf		(2H, t), 1.23 (3H, t)	
	-ethyl)-phenyl]-amide	onamide			
I	2-(4-chloro-phenyl)-7-hydro	aniline	0	6 8.18 (2H, d), 8.11 (1H, d), 7.80 (2H, d), 7.67 (2H,	363
	xy-1H-benzoimidazole-4-carb			d), 7.40 (2H, t), 7.15 (1H, t), 6.89 (1H, d)	
	oxylic acid phenylamide				

15	2	2-(4-chloro-phenyl)-7-hydro	4-hydroxycycl (	0	6 8.15 (2H, d), 7.84 (1H, d), 7.69 (2H, d), 6.90 (1H,	385
		xy-1H-benzoimidazole-4-carb	ohexylamine		d), 3.95 (1H, m), 3.58 (1H, m), 2.28-1.95 (4H, m),	
		oxylic acid (4-hydroy-			1.83-1.25 (4H, m)	
	_	cyclohexyl)-amide				
16	2	2-(4-chloro-phenyl)-7-hydro	N-[2-(4-amin	0	6 8.18 (2H, d), 7.98 (1H, d), 7.80-7.60 (6H, m), 7.36	560
		xy-1H-benzoimidazole-4-carb	o-phenyl)-eth		(2H, d), 7.16 (2H, d), 6.94 (1H, d), 3.09 (2H, t), 2.74	
	·	oxylic acid (4-[2-(toluene-4-	yl]-4-methyl-		(2H, t), 2.41 (3H, s)	
		sulfonylamino)-ethyl]-phenyl}	benzensulfona			
		-amide	mide			
17	2	2-(4-chloro-phenyl)-7-hydro	N-[2-(4-amin (	0	6 8.15 (1H, d), 7.94 (1H, d), 7.72 (2H, d), 7.62 (2H,	484
		xy-1H-benzoimidazole-4-carb	o-phenyl)-eth		d), 7.28 (2H, d), 6.85 (1H, d), 3.32 (2H, t), 2.85	-
		oxylic acid	yl]-methenesul		(3H,s), 2.84 (2H, t)	
		[4-(2-methanesulfonylamino-e	fonylamide			
· ·		thyl)-phenyl]-amide				
18	2	2-(4-chloro-phenyl)-7-hydro	2-[2-(4-amino   C	0	8 8.16 (2H, d), 8.02 (1H, d), 7.86-7.76 (4H, m),	536
		xy-1H-benzoimidazole-4-carb	-phenyl)-ethyl		7.75-7.61 (4H, m), 7.22 (2H, d), 6.95 (1H, m), 3.90	
		oxylic acid (4-[2-(1,3-dioxo	]-isoindole-1,		(2H, t), 2.97 (2H, t)	
		-1,3-dihydro-isoindole-2-yl)-	3-dione			_
		ethyl]-phenyl}-amide				
				$\neg$		

19	2	2-(4-chloro-phenyl)-7-hydro	thiophene-2-	0	8 8.15 (2H, d), 7.97 (2H, d), 7.75-7.57 (6H, m), 7.19	552
		xy-1H-benzoimidazole-4-carb	sulfonic		(2H, d), 6.92 (1H, d), 3.17 (2H, t), 2.77 (2H, t)	
		oxylic acid	acid[2-(4-amin			
		{4-[2-(thiophene-2-sulfonyla	o-phenyl)-eth			
		mino-ethyl)-phenyl]-amide	yl]-amide			
50	2	2-(4-chloro-phenyl)-7-hydro	N-[2-(4-amin	0	8 8.17 (2H, d), 8.09 (2H, d), 7.73 (2H, d), 7.63 (2H,	498
		xy-1H-benzoimidazole-4-carb	o-phenyl)-eth		d), 7.29 (2H, d), 3.31 (2H, t), 2.98 (2H, q), 2.85 (2H,	
		oxylic acid	yl]-ethanasulf		t), 1.24 (3H, t)	
		[4-(2-ethanesulfonylamino-et	onylamide			
		hyl)-phenyl]-amide				
21	က	2-(2,4-dichloro-phenyl)-7-hy	ammonium	0	6 7.98-7.70 (2H, m), 7.69-7.52 (1H, m), 7.28-7.00	321
		droxy-1H-benzoimidazole-4-c	chloride		(1H, m), 6.95-6.82 (1H, m)	
		arboxylic acid amide				
22	က	2-(2,4-dichloro-phenyl)-7-hy	aniline	0	8 8.02 (1H, d), 8.01-7.82 (1H, m), 7.81-7.65 (3H,	397
		droxy-1H-benzoimidazole-4-c			m), 7.64-7.45 (1H, m), 7.43-7.20 (2H, t), 7.42-7.02	
		arboxylic acid phenylamide			(1H, t), 6.90 (1H, d)	
23	က	2-(2,4-dichloro-phenyl)-7-hy	4-hydroxy-cyc	0	6 8.02-7.68 (2H, m), 7.68-7.48 (1H, m), 7.20-7.03	419
		droxy-1H-benzoimidazole-4-c   lohexylamine	lohexylamine		(1H, m), 6.88 (1H, d), 3.93 (1H, m), 3.58 (1H, m),	
		arboxylic · acid			2.25-1.85 (4H, m), 1.84-1.39 (4H, m)	
		(4-hydroxy-cyclohexyl)-amide	· · · · · · · · · · · · · · · · · · ·			

24	ო	2-(2,4-dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-c arboxylic acid [4-(2-amino-ethyl)-phenyl]-amide	4-aminophenet hylamine	0	6 7.97 (2H, d), 7.85-7.63 (3H, m), 7.56 (1H, d), 7.38-7.20 (2H, m), 6.82 (1H, d), 3.18 (2H, t), 2.96 (2H, t)	440
25	ю	2-(2,4-Dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-c arboxylic acid (4-amino- phenyl)-amide	1,4-phenylene diamine	0	6 8.06-7.81 (4H, m), 7.80-7.64 (1H, s), 7.58 (1H, d), 7.38 (2H, d), 6.84 (1H, d)	412
56	က	2-(2,4-Dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-c arboxylic acid (4-hydroxy methyl-phenyl)-amide	4-aminobenzy (alcohol	0	8 8.00 (1H, d), 7.98-7.84 (1H, m), 7.75 (1H, m), 7.74-7.52 (2H, m), 7.50-7.26 (1H, m), 7.25-7.05 (2H, m), 7.04-6.80 (1H, m)	427
27	က	2-(2,4-Dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-c arboxylic acid [4-(2-hyroxy- ethyl)-phenyl]-amide	4-aminophenet Chyl alcohol	0	6 8.15-7.86 (2H, m), 7.85-7.45 (3H, m), 7.25 (2H, d), 7.20-6.75 (2H, m), 4.58 (1H, t), 3.75 (1H, t), 3.05 (1H, t), 2.81 (1H, t)	441

28	3	2-(2,4-dichloro-phenyl)-7-hy	N-[2-(4-amin (	0 8	8 8.20-8.02 (3H, m), 8.00 (2H, d), 7.70-7.68 (3H,	594
		droxy-1H-benzoimidazole-4-c	o-phenyl)-eth	_=	m), 7.38 (2H, d), 7.16 (2H, d), 6.94 (1H, d), 3.10 (2H,	
		arboxylic	yl]-4-methyl-	<del></del>	t), 2.73 (2H, t), 2.43 (3H, s)	
		{4-[2-(toluene-4-sulfonylami	benzensulfona			
		no)-ethyl]-phenyl}-amide	mide			
29	က	2-(2,4-dichloro-phenyl)-7-hy	<i>N</i> -[2-(4-amin 0	9 0	8 8.02 (1H, d), 8.01-7.78 (1H, m), 7.70 (2H, d),	518
		droxy-1H-benzoimidazole-4-c	o-phenyl)-eth	7.	7.67-7.50 (1H, m), 7.25 (2H, d), 6.90 (2H, d), 3.28	
		arboxylic	yl]-methanesul	(3	(2H, t), 2.84 (2H, t), 2.82 (3H,s)	
		[4-(2-methanesulfonylamino-e	fonamide			
		thyl)-phenyl]-amide		-		
30	က	2-(2,4-dichloro-phenyl)-7-hy	2-[2-(4-amino 0		6 7.10 (1H, d), 6.99-6.81 (6H, m), 6.80-6.65 (3H,	570
		droxy-1H-benzoimidazole-4-c	-phenyl)-ethyl	Î.	m), 6.28 (2H, d), 5.92 (1H, d), 2.88 (2H, t), 1.97 (2H,	
		arboxylic acid	]-isoindole-1,	Ŧ	•	
		{4-[2-(1,3-dioxo-1,3-dihydro	3-dione	·		
		-isoindole-2-yl)-ethyl]-pheny				
		1}amide				
31	က	2-(2,4-dichloro-phenyl)-7-hy	thiophene-2-s 0	<u> </u>	6 8.08 (1H, d), 7.88 (2H, m), 7.83 (1H, d), 7.75 (1H,	586
		droxy-1H-benzoimidazole-4-c ulfonic	ulfonic	<del>'</del> <del>'</del> <del>'</del>	d), 7.68-7.65 (3H, m), 7.63 (1H, d), 7.17-7.01 (2H,	
		arboxylic acid	acid[2-(4-ami	(m	m), 6.97 (1H, d), 3.16 (2H, t), 2.77 (2H, t)	
		[4-[2-(thiophene-2-sulfonyla	no-phenyl)-eth			
		mino)-ethyl]-phenyl}-amide	yl]-amide			

32	က	2-(2,4-dichloro-phenyl)-7-hy	N-[2-(4-amin (	0	6 8.11 (1H, d), 7.95-7.82 (2H, m), 7.75-7.60 (3H, 532
		drioxy-1H-benzoimidazole-4-	o-phenyl)-eth		m), 7.28 (2H, d), 7.01 (1H, d), 3.31 (2H, t), 2.98 (2H,
		carboxylic acid [4-(2-	yl]-ethanesulf		q), 2.85 (2H, t), 1.24 (3H, t)
		ethanesulfonylamino-ethyl)-ph	onamide	·	
		enyl]-amide			
33	4	2-(4-fluoro-phenyl)-7-hydrox	N-[2-(4-amin (	0	8 8.23-8.15 (2H, m), 7.91 (1H, d), 7.69 (2H, d), 7.39
		y-1H-benzoimidazole-4-carbo	o-phenyl)-eth		(2H, t), 7.26 (2H, d), 6.83 (1H, d), 3.31 (2H, t),
		xylic acid [4-(2-methane	yl]-methanesul		2.85-2.78 (5H, m)
		sulfonylamino-ethyl)-phenyl]-	fonamide		
		amide		·	
34	4	2-(4-fluoro-phenyl)-7-hydrox	N-[2-(4-amin 0	0	8 8.25-8.21 (2H, m), 7.98-7.93 (2H, m), 7.71-7.64
		y-1H-benzoimidazole-4-carbo	o-phenyl)-eth		(4H, m), 7.41-7.34 (3H, m), 7.14 (2H, d), 6.87 (1H,
		xylic acid {4-[2-	yl]-4-methyl-		d), 3.08 (2H, t), 2.73 (2H, t), 2.40 (3H, s)
		(toluene~4-sulfonylamino)-eth	benzensulfona	· · · · · ·	
		yl]-phenyl}-amide	mide	<del></del>	
35	4	2-(4-fluoro-phenyl)-7-hydrox	N-[2-(4-amin 0	0	6 8.05 (2H, t), 7.78 (1H, d), 7.30 (2H, t), 7.14 (2H, d),
		y-1H-benzoimidazole-4-carbo	o-phenyl)-eth		6.77 (2H, d), 6.69 (1H, d), 3.78 (2H, q), 3.35 (2H, t),
		xylic acid [4-(2-	yl]-ethanesulf		2.90 (2H, t), 1.28 (3H, t)
		methanesulfonylamino-ethyl)-	onamide		
		phenyl]-amide			

36	4	2-(4-fluoro-phenyl)-7-hydrox	4-morpholin-4	0		
		y-1H-benzoimidazole-4-carbo	-yl-phenylami			-
		xylic acid (4-morpholin-4-	ne			
		yl-phenyl)-amide				_
37	വ	2-(2,4-difluoro-phenyl)-7-hyd N-[2-(4-amin		0	8 7.90 (1H, d), 7.62 (1H, d), 7.31-7.17 (4H, m), 6.81	
		roxy-1H-benzoimidazole-4-ca	o-phenyl)-eth		(1H, d), 3.22 (2H, t), 2.76 (5H,m)	
		rboxylic acid [4-(2-	[4-(2- yl]-methanesul			
		methanesulfonylamino-ethyl)-	fonamide			
		phenyl]-amide			,	·
38	വ	2-(2,4-difluoro-phenyl)-7-hyd	N-[2-(4-amin	0	8 7.99 (1H, m), 7.74 (1H, d), 7.50 (2H, d), 7.33-7.26	
		roxy-1H-benzoimidazole-4-ca	o-phenyl)-eth		(2H, m), 7.23 (4H, m), 6.94 (2H, d), 6.81 (1H, d), 3.58	•
		rboxylic acid (4-[2-(toluene	yl]-4-methyl-		(2H, t), 2.82 (2H, t), 2.23 (3H, s)	
		-4-sulfonylamino)-ethyl]-phe	benzensulfona			
		nyl}amide	mide			
39	5	2-(2,4-difluoro-phenyl)-7-hyd	N-[2-(4-amin (	0	6 8.19-8.00 (2H, m), 7.70 (1H, d), 7.43-7.26 (4H,	
		roxy-1H-benzoimidazole-4-	o-phenyl)-eth		m), 6.87 (1H, d), 3.98 (2H, t), 2.97 (2H, q), 2.86 (2H,	
	_	carboxylic acid [4-(2-methane	yl]-ethanesulf		t), 1.25 (3H, t)	<u>-</u>
		sulfonylamino-ethyl)-phenyl]-	onamide			
		amide				

6 8.01-7.93 (1H, m), 7.65 (3H, t), 7.53-7.44 (2H, m), 7.33 (4H, m), 7.11 (2H, d), 6.80 (1H, d), 3.09 (2H, t), 2.72 (2H, t), 2.38 (3H, s)	8 8.06 (1H, m), 7.97 (1H, d), 7.68-7.61 (3H, m), 7.40 (1H, m), 7.27 (2H, m), 6.97 (1H, m), 3.61 (2H, t), 2.84 (5H, m)	6 8.07 (1H, m), 7.97 (1H, d), 7.68-7.40 (3H, m), 7.28-7.18 (3H, m), 6.99 (1H, d), 3.61 (2H, t), 2.96 (2H, q), 2.84 (2H, t), 1.28 (3H, t)
0	0	0
N-[2-(4-amin o-phenyl)-eth yl]-4-methyl-benzensulfona mide)	N-[2-(4-amin o-phenyl)-eth yl]-methanesul fonamide	N-[2-(4-amin o-phenyl)-eth yl]ethanesulfon amide
2-(2-chloro-4-fluoro-phenyl) N-[2-(4-amin -7-hydroxy-1H-benzoimidazol o-phenyl)-eth e-4-carboxylic acid (4-[2- yl]-4-methyl- (toluene-4-sulfonylamino)-eth benzensulfona yl]-phenyl}amide mide)	2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid [4-(2-methanesulfonylamino-ethyl)- phenyl]-amide	2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid [4-(2-methanesulfonylamino-ethyl)- phenyl]-amide
9	9	Q
40	41	42

43	2	2-(3-chloro-4-fluoro-phenyl)	N-[2-(4-amin (	0	6 8.18 (1H, d), 7.90 (1H, m), 7.72 (1H, d), 7.47 (2H,	
		-7-hydroxy-1H-benzoimidazol	o-phenyl)-eth		d), 7.39 (1H, m), 7.13-7.06 (4H, m), 6.95(2H, d),	
		e-4-carboxylic acid	yl]-4-methyl-		6.75 (1H, d), 3.63 (2H, t), 2.85 (2H, t), 2.23 (3H, s)	
		{4-[2-(toluene-4-sulfonylami	benzensulfona			
		no)-ethyl]-phenyl}amide	mide			i
44	2	2-(3-chloro-4-fluoro-phenyl)	<i>N</i> -[2-(4-amin (	0	8 8.27 (1H, d), 8.10 (1H, m), 7.85 (1H, d), 7.64 (2H,	
		-7-hydroxy-1H-benzoimidazol	o-phenyl)-eth		d), 7.41 (1H, t), 7.22 (2H, d), 6.76 (1H, d), 3.26 (2H,	
		e-4-carboxylic acid	yl]-ethanesulf		t), 2.94 (2H, q), 2.80 (2H, t), 1.22(3H, t)	
	··	[4-(2-methanesulfonylamino-e	onamide	_	,	
		thyl)-phenyl]-amide				
45	7	2-(3-chloro-4-fluoro-phenyl)	N-[2-(4-amin C	0	6 8.31 (1H, d), 8.12 (1H, m), 7.91 (1H, d), 7.68 (2H,	ı
		-7-hydroxy-1H-benzoimidazol	o-phenyl)-eth		d), 7.47 (1H, t), 7.26 (2H, d), 6.83 (1H, d), 3.31 (2H, $)$	
		e-4-carboxylic acid	yl]-methanesul		t), 2.85 (5H, m)	
		[4-(2-methanesulfonylamino-e	fonamide			
		thyl)-phenyl]-amide				
46	-	cyclohexyl-(7-hydroxy-2-phe	piperidine 0	0	6 7.31-7.23 (5H, m), 7.05 (1H, d), 6.64 (1H, d),	320
		nyl-1H-benzoimidazole-4-yl)-			3.53-3.29 (4H, m), 1.82-1.41 (6H, m)	
		methanone				
47	7	2-(4-chloro-phenyl)-7-hydro	piperidine 0		8 8.10 (2H, d), 7.88 (1H, d), 7.66 (2H, d), 6.92 (1H,	355
<del></del>		xy-1H-benzoimidazole-4-carb			d), 3.53-3.29 (4H, m), 1.82-1.41 (6H, m)	
		oxylic acid cyclohexyl-amide				

48	က	2-(2,4-dichloro-phenyl)-7-hy	piperidine	0	8 7.31-7.23 (3H, m), 7.05 (1H, d), 6.64 (1H, d),	389
		droxy-1H-benzoimidazole-4-y			3.53-3.29 (4H, m), 1.82-1.41 (6H, m)	
		1-piperidine-1-yl-methanone				
49	7	7-hydroxy-2-phenyl-1H-benz	4-nitrobenzyla	Ţ	8 8.20 (2H, d), 8.13 (2H, d), 7.82 (1H, d), 7.82-7.55	388
		oimidazole-4-carboxylic	mine-hydrochl		(5H, m), 6.87 (1H, d), 4.75 (2H, s)	
		acid(4-nitro-benzyl)-amide	oride)			
50	1	7-hydroxy-2-phenyl-1H-benz	4-aminobenzyl	-	8 8.15 (2H, d), 7.82 (1H, d), 7.72-7.52 (5H, m), 7.33	358
		oimidazole-4-carboxylic acid	amine-dihydro		(2H, d), 6.87 (1H, d), 4.70 (2H, s)	
		(4-amino-benzyl)-amide	chloride			
51	П	7-hydroxy-2-phenyl-1H-benz	benzylamine	7	8 8.10 (2H, d), 7.87 (1H, d), 7.85-7.60 (3H, m), 7.40	343
		oimidazole-4-carboxylic acid			(2H, d), 7.39-7.28 (2H, m), 7.27-7.20 (1H, m), 6.89	
		benzylamide			(1H, d), 4.66 (2H, s)	
52	2	2-(4-chloro-phenyl)-7-hydro	benzylamine		8 8.10 (2H, d), 7.88 (1H, d), 7.66 (2H, d), 7.42-7.23	377
		xy-1H-benzoimidazole-4-carb			(5H, m), 6.92 (1H, d), 4.68 (2H, s)	
		oxylic acid benzylamide				
53	2	2-(4-chloro-phenyl)-7-hydro	4-nitrobenzyla	-	8 8.20 (2H, d), 7.90 (2H, d), 7.88 (1H, s), 7.69-7.51	422
		xy-1H-benzoimidazole-4-carb	mine-hydrochl		(4H, m), 6.91 (1H, d), 4.76 (2H, s)	
		oxylic acid(4-nitro-benzyl)-	oride			
		amide				

54	2	2-(4-chloro-phenyl)-7-hydro	4-aminobenzyl	1 8 8.20	8 8.20 (2H, d), 7.90 (2H, d), 7.88 (1H, s), 7.69-7.51	392
		xy-1H-benzoimidazole-4-carb	amine-hydroxy	(4H, m	(4H, m), 6.91 (1H, d), 4.76 (2H, s)	
		oxylic acid (4-amino-benzyl)-	chloride			
		amide				
55	က	2-(2,4-dichloro-phenyl)-7-hy	benzylamine 1		6 8.10 (2H, d), 7.88 (1H, d), 7.66 (2H, d), 7.37-7.23	411
		droxy-1H-benzoimidazole-4-c		(4H, m	(4H, m), 6.92 (1H, d), 4.68 (2H, s)	
		arboxylic acid benzylamide				
56	က	2-(2,4-Dichloro-phenyl)-7-hy	4-nitrobenzyla 1		8 8.20 (2H, d), 7.90 (2H, t), 7.88 (1H, s), 7.69-7.51	456
		droxy-1H-benzoimidazole-4-c	mine	(ЗН, ш	(3H, m), 6.91 (1H, d), 4.76 (2H, s)	
		arboxylic acid	_			-
		(4-nitro-benzyl)-amide				
22	<u>~</u>	7-hydroxy-2-phenyl-1H-benz	phenethylamin 2		8 8.10 (2H, d), 7.78 (1H, d), 7.77-7.58 (3H, m),	357
		oimidazole-4-carboxylic acid	υ	7.44-7	7.44-7.18 (5H, m), 6.85 (1H, s), 3.68 (2H, t), 2.98	
		-phenethyl-amide		(2H, t)		
58	<del></del>	7-hydroxy-2-phenyl-1H-benz	4-hydroxyphen 2		6 8.02-7.92 (2H, m), 7.77 (1H, d), 7.62-7.42 (3H,	373
		oimidazole-4-carboxylic acid	ethylamine	m), 7.1	m), 7.11 (2H, d), 6.78 (1H, d), 6.70 (2H, d), 3.72 (2H,	
		(4-hydroxy-pheneethyl)-amid		t), 2.83	t), 2.83 (2H, t)	
		O.				-
59		7-hydroxy-2-phenyl-1H-benz	4-nitropheneth 2	8 8.10	8 8.10 (2H, d), 8.01 (2H, d), 7.75 (1H, d), 7.69-7.52	402
<del></del>		oimidazole-4-carboxylic acid	ylamine	(3H, m)	(3H, m), 7.50 (2H, d), 6.85 (1H, d), 3.75 (2H, t), 3.08	
		(4-nitro-phenethyl)-amide		(2H, t)		

09	-1	7-hydroxy-2-phenyl-1H-benz	4-aminophenet	0	8 8 11 (2H d) 778 (1H d) 774-750 (3H m) 746	370
		oimidazole-4-carboxylic acid		1		9
		(4-amino-phenethyl)-amino			(2H, t)	
61	1	7-hydroxy-2-phenyl-1H-	ethylenediamin	2	6 7.95-7.70 (2H, m), 7.69 (1H, d), 7.60-7.42 (1H,	296
		benzoimidazole-4-carboxylic	Ф		m), 7.41-7.23 (2H, m), 3.77 (2H, t), 3.25 (2H, t)	
		acid (2-amino-ethyl)-amide				
62		7-hydroxy-2-phenyl-1H-	4-hydroxy-3-	2	8 8.10-8.00 (2H, m), 7.78 (1H, d), 7.69-7.52 (3H,	403
		benzoimidazole-4-carboxylic	methoxyphenet		m), 6.91-6.77 (2H, m), 6.72 (2H, d), 3.73 (3H, s),	
		acid (4-hydroxy-3-methoxy-	hylamine		3.70 (2H, t), 2.89 (2H, t)	
		phenethyl)-amide				
63		7-hydroxy-2-phenyl-1H-	3-hydroxy-4-	2	8 8.08-7.93 (2H, m), 7.78 (1H, d), 7.62-7.50 (2H,	403
		benzoimidazole-4-carboxylic	methoxyphenet	· · ·	m), 6.98-6.52 (5H, m), 3.80 (3H, s), 3.68 (2H, t), 2.82	
		acid (3-hydroxy-4-methoxy	hylamine		(2H, t)	
		-phenethyl)-amide				
64	1	7-hydroxy-2-phenyl-1H-	N-[4-(2-amin 2	2	6 8.07 (1H, d), 7.77 (1H, d), 7.65-7.61 (4H, m), 7.28	450
		benzoimidazole-4-carboxylic	o-ethyl)-phen		(2H, d), 7.18 (2H, d), 6.85 (1H, d), 3.71 (2H, t), 2.95	
		acid[2-(4-methanesulfonylami	yl]-methanesul		(2H, t), 2.85 (3H, s)	
		no-phenyl)-ethyl]-amide	fonamide			

65		7-hydroxy-2-phenyl-1H-	N-[4-(2-amin	2 8 8.	6 8.09 (2H, d), 7.76-7.54 (5H, m), 7.33-7.30 (3H.	526
		benzoimidazole-4-carboxylic	o-ethyl)-phen	 田		
	<del></del>	acid{2-[4-(toluene-4-sulfonyl	yl]-4-methyl-	t), 3.	t), 3.63 (1H, t), 3.01 (1H, t), 2.88 (1H, t), 2.44 (3H, s)	
		amino)-phenyl]-ethyl}-amide	benzensulfona	·		
			mide			
99		7-hydroxy-2-phenyl-H-benzo	4-(2-aminoeth	2 8 8.	8 8.17-8.12 (2H, m), 7.88 (1H, d), 7.77-7.71 (3H,	366
		imidazole-4-carboxylic acid	yl) morpholine	m), ?	m), 7.00-6.95 (1H, m), 4.02-3.75 (4H, m), 3.89 (2H,	
		(2-morpholin-4-yl-ethyl)-ami		t), 3.	t), 3.47 (2H, t), 3.46-3.00 (4H, t)	
		de				
29		7-hydroxy-2-phenyl-1H-benz	2-[4-(2-amino 2	<del> </del>	6 8.14 (2H, d), 7.97-7.68 (8H, m), 7.40 (4H, dd),	502
		oimidazole-4-carboxylic	-ethyl)-phenyl	6.93	6.93 (1H, d), 3.74 (2H, t), 3.05 (2H, t)	
		acid{2-[4-(1,3-dioxo-1,3-dih	]-isoindole-1,	····		
		ydro-isoindole-2-yl)-phenyl]-	3-dione			
		ethyl}-amide				
89		7-hydroxy-2-phenyl-1H-benz $N-[4-(2-amin$	N-[4-(2-amin 2	f	6 8.15 (2H, d), 7.79-7.72 (4H, m), 7.22 (4H, dd),	
		oimidazole-4-carboxylic acid	acid o-ethyl)-phen	6.97	6.97 (1H, d), 3.66 (2H, t), 2.99 (2H, q), 2.89 (2H, t),	
		[2-(4-ethanesulfonylamino-ph yl]-ethansulfo	yl]-ethansulfo	1.22	1.22 (3H, t)	
		enyl)-ethyl]-amide	namide			<del></del>

69		7-hydroxy-2-phenyl-1H-benz	2-(2-aminoeth 2	8 8.84 (1H, d), 8.13	\$ 8.84 (1H, d), 8.13-8.05 (3H, m), 7.80-7.65 (4H,	418
		oimidazole-4-carboxylic acid	ylamino)-5-nit	m), 6.90 (1H, d), 6.5	m), 6.90 (1H, d), 6.57 (1H, d), 3.71-3.60 (4H, m)	
		(5-mitropyridine-2-amino-eth	ropyridine			
		yl)-amide			-	
20	<u> </u>	7-hydroxy-2-phenyl-1H-	2-(2-aminoeth 2	8.71 (1H, d), 8.44 (	8.71 (1H, d), 8.44 (1H, t), 8.13-7.99 (4H, m), 7.85	358
		benzoimidazole-4-carboxylic	yl)-pyridine	(1H, t), 7.76-7.70 (2	(1H, t), 7.76-7.70 (2H, m), 6.99 (1H, d), 6.83 (1H, d),	
		acid (2-pyridine-2-yl-ethyl)		3.97 (2H, t), 3.42 (2H, t)	H, t)	
		-amide				
71	2	2-(4-chloro-phenyl)-7-hydro	phenethylamin 2	8 8.03 (2H, d), 7.79	6 8.03 (2H, d), 7.79 (1H, d), 7.64 (2H, m), 7.37-7.15	391
		xy-1H-benzoimidazole-4-carb	υ	(5H, m), 6.84 (1H, d)	(5H, m), 6.84 (1H, d), 3.75 (2H, t), 2.99 (2H, t)	
		oxylic acid phenethyl amide				
72	2	2-(4-chloro-phenyl)-7-hydro	4-nitropheneth 2	6 8.18 (2H, d), 8.05	6 8.18 (2H, d), 8.05 (2H, d), 7.80 (1H, d), 7.64 (2H,	436
		xy-1H-benzoimidazole-4-carb	ylamine	d), 7.56 (2H, d), 6.88	d), 7.56 (2H, d), 6.88 (1H, d), 3.80 (2H, t), 3.11 (2H,	
		oxylic acid (4-nitro-phenethyl)		t)		
		-amide				
73	2	2-(4-chloro-phenyl)-7-	4-aminophenet 2	5 8.11 (2H, d), 7.83	5 8.11 (2H, d), 7.83 (1H, d), 7.64 (2H, d), 7.50 (2H,	406
		hydroxy-1H-benzoimidazole-4	hylamine	d), 7.31 (2H, d), 6.82	d), 7.31 (2H, d), 6.82 (1H, d), 3.78 (2H, t), 3.07 (2H,	
		-carboxylic acid (4-amino-		t)		
		phenethy!)-amide				

74	2	2-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb oxylic acid (4-hydroxy- phenethyl)-amide	4-hydroxyphen 2 ethylamine	2	67.82 (1H, d), 7.73 (2H, d), 7.65 (2H, d), 7.12 (2H, d), 7.00 (1H, d), 6.86 (1H, d), 6.74 (1H, d), 3.71 (2H, t), 2.87 (2H, t)	407
75	0	2-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb oxylic acid [2-(4-methane sulfonylamino-phenyl)-ethyl]- amide	N-[4-(2-amin o-ethyl-phenyl )-methanesulfo namide	8	5 8.08 (2H, d), 7.79 (1H, d), 7.69 (2H, d), 7.29-7.16 (4H, dd), 6.89 (1H, d), 3.71 (2H, t), 2.95 (2H, t), 2.88 (3H, s)	484
92	2	2-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb oxylic acid {2-[4-(toluene-4 -sulfonylamino)-phenyl]-ethyl }-amine	N-[4-(2-amin 2 o-ethyl)-phen yl]-4-methyl- benzenesulfona mide	2 2 3	6 8.08 (2H, d), 7.77 (1H, d), 7.69 (2H, d), 7.55 (1H, d), 7.15 (3H, m), 6.98 (2H, d), 6.88 (1H, d), 3.65 (2H, t), 2.86 (2H, t), 2.31 (3H, s)	560
77	2	2-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb oxylic acid (3-hydroxy-4- methoxy-phenethyl)-amide	3-hydroxy 2 -4-methoxy-p henethylamine		6 8.10-7.37 (3H, m), 7.36-6.43 (6H, m), 3.72 (3H, s), 3.70 (2H, t), 2.81 (2H, t)	437

82	8	2-(4-chloro-phenyl)-7-hydro	2-(2-aminoeth 2	2	8 8.70 (1H, d), 8.43 (1H, t), 8.13-8.09 (3H, m), 8.01   39	392
	- <u> </u>	xy-1H-benzoimidazole-4-carb yl)-pyridine	yl)-pyridine			
		oxylic acid (2-pyridine-2-yl-			(2H, t), 3.42 (2H, t)	_
		ethyl)-amide				
83	2	2-(4-chloro-phenyi)-7-hydro	histamine 2	2	6 8.81(s, 1H), 8.12(d, 2H), 7.80(d, 1H), 7.65(d, 2H),	
		xy-1H-benzoimidazole-4-carb		·	7.40(s, 1H), 6.83(d, 1H), 3.84(t, 2H), 3.12(t, 2H)	
		oxylic acid [2-(1H-imidazol-4				
		-yl)-ethyl]amide				
84	2	2-(4-chloro-phenyl)-7-hydro	4-hydroxyphen 2	$\vdash$	8 8.05(d, 2H), 7.79(d, 1H), 7.65(d, 2H), 7.12(d, 2H),	
		xy-1H-benzoimidazole-4-carb	ethylamine		6.85(d, 1H), 6.72(d, 2H), 3.70(t, 2H), 2.87(t, 2H)	
		oxylic acid [2-(4-hydroxy				
		-phenyl)-ethyl]-amide				
85	2	2-(4-Chloro-phenyl)-7-hydro	4-acetyl-2-py 2	1	8 8.57(s, 1H), 8.20~8.00(m, 3H), 8.02(br, 1H),	
		xy-1H-benzoimidazole-4-carb	ridylethylamine		$7.75 \sim 7.60(m, 3H), 7.38(d, 1H), 6.88(d, 1H), 4.12(t, )$	
		oxylic acid [2-(5-acetylamino			2H), 3.68(t, 2H), 2.12(s, 3H)	
		-pyridin-2-ylamino)-ethyl]-a				
		mide				

98	2	2-(4-chloro-phenyl)-7-hydro	N-[4-(2-amin 2	6 8.03(m, 2H), 7.80(d, 1H), 7.60(d, 2H), 7.57(d, 2H),
		xy-1H-benzoimidazole-4-carb o-ethyl)-phen	o-ethyl)-phen	7.29(d, 2H), 6.83(d, 1H), 3.75(t, 2H), 3.34(s, 2H),
		oxylic acid $(2-\{4-[2-(4-y]]-2-(4-meth)\}$	yl]-2-(4-meth	3.10~2.75(m, 13H)
		methyl-piperazin-1-yl)-acetyl	yl-piperazin-1	
		amino]-phenyl}-ethyl)-amide	-yl)-acetamide	
87	2	2-(4-chloro-phenyl)-7-hydro	N-[4-(2-amin 2	8 8.03(m, 2H), 7.79(d, 1H), 7.61(d, 2H), 7.53(d, 2H),
		xy-1H-benzoimidazole-4-carb o-ethyl)-phen	o-ethyl)-phen	7.29(d, 2H), 6.84(d, 1H), 3.75(t, 2H), 3.34(s, 2H),
		oxylic acid $(2-\{4-[2-(4-y]]-2-(4-ethy]]$	yl]-2-(4-ethyl	3.25(q, 2H), 3.05~2.75(m, 8H), 1.35(t, 3H
		ethyl-piperazin-1-yl)-acetyla	-piperazin-1-y	
		mino]-phenyl}-ethyl)-amide	I)-acetamide	
88	2	2-(4-chloro-phenyl)-7-hydro	N-[4-(2-amin 2	8 8.03(d, 2H), 7.80(d, 1H), 7.60(d, 2H), 7.54(t, 2H),
		xy-1H-benzoimidazole-4-carb	o-ethyl)-phen	7.32(d, 2H), 6.81(d, 1H), 4.08(s, 2H), 3.76(t, 2H),
		oxylic acid (2-[4-(2-	{2-[4-(2- yl]-2-dimethyl	2.95(m, 8H)
		dimethylamino-acetylamino)-p amino-acetami	amino-acetami	
		henyl]-ethyl}-amide	de	

68	2	2-(4-chloro-phenyl)-7-hydro	N-[4-(2-amin   2	8 8.02(d, 2H), 7.80(d, 1H), 7.60(d, 2H), 7.54(d, 2H),
		xy-1H-benzoimidazole-4-carb	o-ethyl)-phen	7.32(d, 2H), 6.81(d, 1H), 4.06(s, 2H), 3.77(t, 2H),
		oxylic acid {2-[4-(2-	(2-[4-(2- yl]-2-diethyla	3.32(q, 4H), 2.99(t, 2H), 1.35(t, 6H)
		diethylamino-acetylamino)-phe mino-acetamid	mino-acetamid	
		nyl]-ethyl}-amide	۵	
06	2	2-(4-chloro-phenyl)-7-hydro	4-aminophenet 2	8 8.13(d, 2H), 7.78(d, 1H), 7.62(d, 2H), 7.51(d, 2H),
		xy-1H-benzoimidazole-4-carb	hylamine	7.29(d, 2H), 6.77(d, 1H), 3.79(t, 2H), 3.69(t, 2H
		oxylic acid [2-(4-amino		. ,
		-phenyl)-ethyl]-amide		
91	2	2-(4-chloro-phenyl)-7-hydro	N-(2-amino-et 2	8 8.73(s, 1H), 8.22(d, 1H), 8.09(d, 1H), 7.88(m, 2H),
		xy-1H-benzoimidazole-4-carb	hyl)-pyridine-	7.60(d, 1H), 7.47(d, 1H), 7.13(d, 1H), 6.78(m, 1H),
		oxylic acid [2-(5-amino	2,5-diamine	3.87(t, 2H), 3.75(t, 2H)
	-	-pyridin-2-ylamino)-ethyl]-a		
		mide		
85	2	2-(4-chloro-phenyl)-7-hydro	<i>N</i> -[4-(2-amin 2	5 8.03(d, 2H), 7.80(d, 1H), 7.60(d, 2H), 7.54(d, 2H),
		xy-1H-benzoimidazole-4-carb	o-ethyl)-phen	7.31(d, 2H), 6.81(d, 1H), 3.12(s, 2H), 3.98(br, 4H),
	_	oxylic acid {2-[4-(2-morpholin   yl]-2-morpholi	yl]-2-morpholi	3.77(t, 2H), 3.44(br, 4H), 2.98(t, 2H)
<del> •</del>		-4-yl-acetylamino)-phenyl]-e	n-4-yl-acetam	
		thyl}-amide	ide	

N/N-(dimethyl 2 6 8.13(d, 2H), 7.78(d, 1H), 7.62(d, 2H), 7.51(d, 2H), amino)pheneth 7.29(d, 1H), 6.77(d, 1H), 3.81(t, 2H), 3.15(s, 6H), 3.08(t, 2H)	2-[4-(2-morp 2 6 8.06(d, 2H), 7.79(d, 1H), 7.73(d, 2H), 7.28(d, 2H), holin-4-yl-eth 6.94(d, 2H), 6.83(d, 1H), 4.31(m, 2H), 3.99(br, 2H), oxy)-phenyl]- 3.95~3.65(m, 4H), 3.65~3.50(m, 4H), 3.32(m, 2H), ethylamine 2.95(m, 2H)	2-{4-[2-(4-m 2 6 8.17(d, 2H), 7.78(d, 1H), 7.40(t, 2H), 7.23(d, 2H), ethyl-piperazin 6.90(m, 3H), 4.25(t, 2H), 3.67(t, 2H), 3.50~3.30(m, -1-yl)-ethoxy 10H), 2.90(m, 5H)  ]-phenyl}-eth ylamine	2-hydroxyphen 2 6 8.05(d, 2H), 7.79(d, 1H), 7.62(d, 2H), 7.18(d, 1H), ethylamine 07.05(d, 1H), 6.90~6.70(m, 3H), 3.70(t, 2H), 3.02(t, 2H)
2-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb oxylic acid [2-(4-dimethyl amino-phenyl)-ethyl]-amide	2-(4-chloro-phenyl)-7-hydro xy-1H-benzoimidazole-4-carb oxylic acid {2-[4-(2-morpholin -4-yl-ethoxy)phenyl]-ethyl}- amide	2-(4-chloro-phenyl)-7-hydro 2-(4-[2 xy-1H-benzoimidazole-4-carb ethyl-pi oxylic acid (2-(4-[2-(41-yl)-methyl-piperazin-1-yl)ethoxy] ]-pheny -phenyl}-ethyl)-amide ylamine	2-(4-chloro-phenyl)-7-hydro 2-hydroxy, xy-1H-benzoimidazole-4-carb ethylamine oxylic acid [2-(2-hydroxy
2	2	0	8
69	94	92	96

97	2	2-(4-chloro-phenyl)-7-hydro	2-methoxyphe	2	6 8.00(d, 2H), 7.81(d, 1H), 7.57(d, 2H), 7.24(d, 1H),	
		xy-1H-benzolmidazole-4-carb oxylic acid [2-(2-methoxy	netnylamine		5.95(m, 1H), 6.65(m, 1H), 6.75(d, 2H), 5.76(s, 5H), 3.64(t, 2H), 2.98(t, 2H)	
		-phenyl)-ethyl]-amide				
86	2	2-(4-chloro-phenyl)-7-hydro	3-bromophene	2	8 8.00(d, 2H), 7.79(d, 1H), 7.02~7.50(m, 3H),	
		xy-1H-benzoimidazole-4-carb	thylamine		7.40~7.20(m, 3H), 6.74(d, 1H), 3.81(t, 2H), 3.01(t,	
		oxylic acid [2-(3-bromo-			2H)	
		phenyl)-ethyl]-amide				
66	က	2-(2,4-dichloro-phenyl)-7-hy	phenethylamin	2	6 7.92-7.66 (3H, m), 7.65-7.38 (1H, m), 7.37-7.00	425
		droxy-1H-benzoimidazole-4-c	Φ		(5H, m), 7.44-7.18 (5H, m), 6.85 (1H, d), 3.68 (2H, t),	
		arboxylic acid phenethyl-amide			2.98 (2H, t)	
100	က	2-(2,4-dichloro-phenyl)-7-	4-nitropheneth	2	6 8.08 (2H, d), 7.90-7.31 (5H, m), 7.20-6.97 (1H,	470
		hydroxy-1H-benzoimidazole-4	ylamine		m), 6.82 (1H, d), 3.76 (2H, t), 3.09 (2H, t)	
		-carboxylic acid(4-amino-				
		phenethyl)-amide				
101	3	2-(2,4-dichloro-phenyl)-7-	4-hydroxy-3-	2	6 7.95-7.68 (3H, m), 7.67-7.40 (2H, m), 7.20-6.92	471
		hydroxy-1H-benzoimidazole-4	methoxyphenet		(1H, m), 6.82 (2H, t), 6.68 (1H, d), 3.72 (2H, t), 3.60	
	_	-carboxylic acid (4-hydroxy	hylamine		(3H, s), 2.88 (2H, t)	
		-3-methoxy-phenethyl)-amide		· · · · · · · · · · · · · · · · · · ·		

102	လ	2-(2,4-dichloro-phenyl)-7- hydroxy-1H-benzoimidazole-4 -carboxylic acid (3-hydroxy	3-hydroxy-4- methoxyphenet hylamine	8	8 8.10-7.37 (3H, m), 7.36-6.43 (6H, m), 3.72 (3H, s), 3.70 (2H, t), 2.81 (2H, t)	471
103	m	2-(2,4-dichloro-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid (2-amino-ethyl)-amide	ethylenediamin e	23	6 8.10 (2H, d), 7.88 (1H, d), 7.66 (2H, d), 7.37-7.23 (4H, m), 6.92 (1H, d), 3.77 (2H, t), 3.25 (2H, t)	364
104	က	2-(2,4-dichloro-phenyl)-7- hydroxy-1H-benzoimidazole-4 -carboxylic acid (4-hydroxy phenethyl)-amide	4-hydroxyphen ethylamine	2	6 7.94-7.64 (3H, m), 7.62-7.39 (1H, m), 7.28-6.97 (3H, m), 6.96-6.78 (1H, m), 6.68 (1H, d), 3.64 (2H, t), 2.82 (2H, t)	441
105	3	2-(2,4-dichloro-phenyl)-7- hydroxy-1H-benzoimidazole-4 -carboxylic acid {2-[4- (toluene-4-sulfonylamino)-phe nyl]-ethyl}-amide	N-[4-(2-amin o-ethyl)-phem phenyl]-4-met hyl-benzensulf onamide	2	6 7.95-7.70 (2H, m), 7.69-7.43 (3H, m), 7.42-7.23 (3H, m), 7.22-7.03 (2H, m), 7.01 (1H, d), 6.98-6.77 (2H, m), 3.81-3.52 (2H, m), 3.10-2.73 (2H, m), 3.01 (1H, t), 2.88 (1H, t), 2.48 (3H, s)	594

106	г С	2-(2,4-dichloro-phenyl)-7-	N-[4-(2-amin	2	6 7.92-7.78 (3H, m), 7.68 (1H, d), 7.24 (4H, dd).	518
		hydroxy-1H-benzoimidazole-4	o-ethyl)-phen		6.96 (1H, d), 3.68 (2H, t), 2.93 (2H, t), 2.90 (3H, s)	
		-carboxylic acid	yl]-methanesul			·
		[2-(4-methanesulfonylamino-p fonamide	fonamide			
		henyl)-ethyl]-amide		• • •		
107	3	2-(2,4-dichloro-phenyl)-7-	2-[4-(2-amino 2	2	6 7.92-7.83 (7H, m), 7.67 (1H, d), 7.38 (4H, dd),	570
		hydroxy-1H-benzoimidazole-4	-ethyl)-phenyl		6.98 (1H, d), 3.72 (2H, t), 3.05 (2H, t)	, 
		-carboxylic acid (2-[4-(1,3	]-isoindole-1,			
		-dioxo-1,3-dihydro-isoindol-2	3-dione			
		-yl)-phenyl]-ethyl}-amide				
108	33	2-(2,4-dichloro-phenyl)-7-	4-(2-aminoeth	2	8 8.02-7.80 (3H, m), 7.65 (1H, d), 6.98 (1H, d),	434
		hydroxy-1H-benzoimidazole-4	yl) morpholine	<del></del> -	4.14-3.92 (2H, m), 3.88 (2H, t), 3.89-3.72 (2H, m),	
		-carboxylic acid (2- morpholin			3.84-3.57 (2H, m), 3.44 (2H, t), 3.30-3.04 (2H, m)	
		-4-yl-ethyl)-amide		·	•	
109	3	2-(2,4-dichloro-phenyl)-7-	N-[4-(2-amin   2	2	6 7.91-7.75 (3H, m), 7.68 (1H, d), 7.21 (4H, dd),	532
		hydroxy-1H-benzoimidazole-4	o-ethyl)-phen		6.99 (1H, d), 3.66 (2H, t), 2.99 (2H, q), 2.89 (2H, t),	
		-carboxylic acid [2-(4-	yl]-ethanesulf		1.28 (3H, t)	
		ethanesulfonylamino-phenyl)-e	onamide			
		thyl]-amide				

110	က	2-(2,4-dichloro-phenyl)-7-hy 2-(2-amin droxy-1H-benzoimidazole-4-c ylamino)-5 arboxylic acid (5- nitropyridine ropyridine -2-amino-ethyl)-amide	oeth	2	6 8.83 (1H, d), 8.11-8.05 (1H, m), 7.86-7.81 (3H, m), 7.68-7.60 (1H, m), 6.90 (1H, d), 6.60-6.54 (1H, d), 3.71-3.60 (4H, m)	486
111	8	2-(2,4-dichloro-phenyl)-7- hydroxy-1H-benzoimidazole-4 -carboxylic acid (2-pyridin -2-yl-ethyl)-amide	2-(2-aminoeth 2yl)-pyridine	2	6 8.70 (1H, d), 8.40 (1H, t), 8.07-7.50 (6H, m), 6.83 (1H, d), 3.95 (2H, t), 3.38 (2H, t)	426
112	3	2-(2,4-dichloro-phenyl)-7-hy 4-(acetylamino droxy-1H-benzoimidazole-4-c )phenethylamin arboxylic acid [2-(4-acetyl e amino-phenyl)-ethyl]-amide		8	6 7.85~7.78(m, 3H), 7.61(d, 1H), 7.25(d, 2H), 7.15(d, 2H), 6.86(d, 1H), 3.69(t, 2H), 2.95(t, 2H), 2.88(s, 3H)	
113	3	2-(2,4-dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-c arboxylic acid [2-(4-pentanoyl amino-phenyl)ethyl]-amide	4-(pentanoyla 2 mino)phenethyl amine	2	6 7.90~7.80(m, 3H), 7.72(d, 1H), 7.61(d, 2H), 7.20(d, 2H), 6.89(d, 1H), 3.68(t, 2H), 2.89(t, 2H), 2.35(t, 2H), 1.65(m, 2H), 1.38(m, 2H), 0.96(t, 3H)	

114	4	2-(4-fluoro-phenyl)-7-hydrox	N-[4-(2-amin   2	8 8.15-8.10 (2H, m), 7.78 (1H, d), 7.46 (2H, t), 7.27
		y-1H-benzoimidazole-4-carbo	o-ethyl)-phen	(2H, d), 7.18 (2H, d), 6.87 (1H, d), 3.70 (2H, t), 2.97
		xylic acid [2-(4-methane	yl]-methanesul	(2H, t), 2.87 (3H, s)
		sulfonylamino-phenyl)-ethyl]-	fonamide	
		amide		
115	4	2-(4-fluoro-phenyl)-7-hydrox N-[4-(2-amin	<i>N</i> -[4-(2-amin 2	
		y-1H-benzoimidazole-4-carbo o-ethyl)-phen	o-ethyl)-phen	
		xylic acid {2-[4-(toluene-4- yl]-p-toluenes	yl]-p-toluenes	
		sulfonylamino)-phenyl]-ethyl}	ulfonamide	
		-amide		
116	4	2-(4-fluoro-phenyl)-7-hydrox N-[4-(2-amin	N-[4-(2-amin 2	8 8.17 (2H, m), 7.77 (1H, d), 7.44 (2H, t), 7.25 (2H,
		y-1H-benzoimidazole-4-carbo	o-ethyl)-phen	d), 7.17 (2H, d), 6.92 (1H, d), 3.67 (2H, t), 3.02 (2H,
<u>-</u>		xylic acid [2-(4-ethanesulfonyl yl]-ethanesulf	yl]-ethanesulf	q), 2.96 (2H, t), 1.26 (3H, t)
		amino-phenyl)-ethyl]-amide	onamide	
117	4	2-(4-fluoro-phenyl)-7-hydrox N-[4-(2-amin	N-[4-(2-amin 2	8 8.1~8.2 (m, 2H), 7.58 (d,1H), 7.44 (m, 4H),
		y-1H-benzoimidazole-4-carbo	o-ethyl)-phen	7.34 (m, 2H), 6.92 (d, 1H), 3.66 (t, 2H), 2.90 (t,
		xylic acid [2-(4-acetylamino	yl]-acetamide	2H), 2.09 (s, 1H)
	-	-phenyl)-ethyl]-amide		

(s)	1),	(a) (d)	D,
6 8.25~8.16(m, 2H), 8.05(d, 1H), 7.48~7.37(m, 2H), 6.88(d, 1H), 3.70~3.50(m, 10H), 3.14(t, 2H), 2.96(s, 3H), 2.12(t, 2H)	6 8.22(m, 2H), 7.85(d, 1H), 7.41(t, 2H), 6.90(d, 1H), 4.20~3.60(m, 8H), 3.48(t, 2H), 3.34~3.10(br, 2H)	5 8.08(m, 2H), 7.74(d, 1H), 7.45(d, 2H), 7.35(t, 2H), 7.18(d, 2H), 6.86(d, 1H), 3.66(t, 2H), 2.86(t, 2H), 2.33(t, 2H), 1.64(m, 2H), 1.39(m, 2H), 0.93(t, 3H)	6 8.14(m, 2H), 7.78(d, 1H), 7.44(t, 2H), 7.09(d, 2H), 6.89(d, 1H), 6.72(d, 2H), 3.66(t, 2H), 2.86(t, 2H)
2	23	2	0
2-(4-methyl-p iperazin-1-yl) -ethylamine	2-morpholin-4 -yl-ethylamine	pentanoic acid [4-(2-amino-e thyl)-phenyl]- amide	4-hydroxyphen ethylamine
2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [2-(4-methyl-piperazin-1-yl)-ethyl]-amide	2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid (2-morpholin -4-yl-ethyl)-amide	2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [2-(4-pentanoyl amino-phenyl)-ethyl]-amide	2-(4-fluoro-phenyl)-7-hydrox 4-hydroxyphen y-1H-benzoimidazole-4-carbo ethylamine xylic acid [2-(4-hydroxy -phenyl)-ethyl]-amide
4	4	<b>ት</b>	4
118	119	120	121

122	4	2-(4-fluoro-phenyl)-7-hydrox	N-(5-nitro-pyr	2	8 8.84(s, 1H), 8.21~8.17(m, 3H), 7.79(d, 1H), 7.44(t.
		y-1H-benzoimidazole-4-carbo	idin-2-yl)-eth		2H), 6.92(d, 1H), 6.63(br, 1H), 3.90~3.60(m, 4H)
		xylic acid [2-(5-nitro-pyridin	ane-1,2-diami		
		-2-ylamino)-ethyl]-amide	ne		
123	4	2-(4-fluoro-phenyl)-7-hydrox	N-[6-(2-Amin	2	6 8.24~8.19(m, 2H), 7.95~7.75(m, 3H), 7.43(t, 2H),
		y-1H-benzoimidazole-4-carbo	o-ethylamino)-		7.15(d, 1H), 6.92(d, 1H), 3.80 $\sim$ 3.65(m, 4H), 2.99(t,
		xylic acid [2-(5-methane	pyridin-3-yl]-		3H)
		sulfonylamino-pyridin-2-ylami	methanesulfon		
		no)-ethyl]-amide	amide		
124	4	2-(4-fluoro-phenyl)-7-hydrox N-[6-(2-amin	<del> </del>	2	6 8.23(m, 2H), 7.81(d, 1H), 7.52(m, 4H),
		y-1H-benzoimidazole-4-carbo	o-ethylamino)-		$7.40 \sim 7.20$ (m, 4H), $7.01$ (d, 1H), $6.82$ (d, 1H), $3.75$ (t,
		xylic acid (2-[5-(toluene-	pyridin-3-yl]-		2H), 3.66(t, 2H), 2.36(s, 3H)
		4-sulfonylamino)-pyridin-2-yl	p-toluenesulfo		
		amino]-ethyl}-amide	namide		
125	4	2-(4-fluoro-phenyl)-7-hydrox	histamine 2	2	6 8.81(s, 1H), 8.19(m, 2H), 7.80(d, 1H),
		y-1H-benzoimidazole-4-carbo			7.50~7.30(m, 3H), 6.90(d, 1H), 3.80(t, 2H), 3.11(t,
		xylic acid [2-(1H-imidazol-			2H)
		4-yl)-ethyl]-amide	-		
1				_	

126	4	2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo	N-[6-(2-amin 2 o-ethylamino)-	6 8.58(s, 1H), 8.22(m, 2H), 8.04(br, 1H), 7.69(d, 1H), 7.50~7.35(m, 3H), 6.90(d, 1H), 4.11(t, 2H), 3.69(t,
<del></del>		xylic acid [2-(5-acetylamino -pyridin-2-yl-amino)-ethyl]-a	pyridin-3-yl]- acetamide	2H), 2.11(s, 3H)
		mide		
127	4	2-(4-fluoro-phenyl)-7-hydrox N-[4-(2-amin	<i>N</i> -[4-(2-amin 2	8 8.10~7.80(m, 2H), 7.69(d, 1H), 7.43(d, 2H), 7.25(t,
		y-1H-benzoimidazole-4-carbo	o-ethyl)-phen	2H), 7.19(d, 2H), 6.76(d, 1H), 3.63(t, 2H), 3.21(s,
		xylic acid (2-{4-[2-(4-	yl]-2-(4-meth	2H), 2.90~2.78(m, 13H)
		methyl-piperazin-1-yl)-acetyl	yl-piperazin-1	
		amino J-phenyl }-ethyl )-amide	-yl)-acetamide	
128	4	2-(4-fluoro-phenyl)-7-hydrox	<i>N</i> -[4-(2-amin   2	8 8.13(m, 2H), 7.79(d, 1H), 7.52(d, 2H), 7.37(t, 2H),
		y-1H-benzoimidazole-4-carbo	o-ethyl)-phen	7.27(d, 2H), 6.85(d; 1H), 3.72(t, 2H), 3.30(s, 2H),
		xylic acid (2-{4-[2-(4-ethyl	yl]-2-(4-ethyl	3.24(q, 2H), 3.05~2.85(m, 10H), 1.35(t, 3H)
		-piperazin-1-yl)-acetylamino]	-piperazin-1-y	
		-phenyl}-ethyl)-amide	1)-acetamide	
129	4	2-(4-fluoro-phenyl)-7-hydrox   N-[4-(2-amin	<i>N</i> -[4-(2-amin   2	8 8.11(m, 2H), 7.78(d, 1H), 7.53(d, 2H),
		y-1H-benzoimidazole-4-carbo	o-ethyl)-phen	7.40~7.25(m, 4H), 6.83(d, 1H), 4.09(s, 2H), 3.74(t,
		xylic acid {2-[4-(2-dimethyl	yl]-2-dimethyl	2H), 2.94(m, 8H)
		amino-acetylamino)-phenyl]-	amino-acetami	
		ethyl}-amide	de	

y-1H-benzoimidazole-4-carbo xylic acid {2-[4-(2-diethyl] amino-acetylamino)-phenyl]-e thyl}-amide  2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [2-(4-amino- phenyl)-ethyl]-amide  4	2-(4-fluoro-phenyl)-7-hydrox N-[4-(2-amin	2 6 8.13(m, 2H), 7.79(d, 1H), 7.54(d, 2H), 7.39(t, 2H).	7.54(d. 2H), 7.39(t. 2H).
xylic acid {2-[4-(2-diethyl amino-acetylamino)-phenyl]-e thyl}-amide  2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [2-(4-amino-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [2-(4-morpholin -4-yl-phenyl)-ethyl]-amide  4	oo o-ethyl)-phen	7.30(d, 2H), 6.86(d, 1H), 4.08(s, 2H), 3.72(t, 2H),	.08(s, 2H), 3.72(t, 2H),
amino-acetylamino)-phenyl]-e thyl}-amide  2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [2-(4-amino- phenyl)-ethyl]-amide  2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [2-(4-morpholin -4-yl-phenyl)-ethyl]-amide  4	yl]-2-diethyla	3.33(q, 4H), 2.96(t, 2H), 1.35(t, 6H)	5(t, 6H)
thyl}-amide  2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [2-(4-amino- phenyl)-ethyl]-amide  4	-e mino-acetamid		
4 2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [2-(4-amino- phenyl)-ethyl]-amide 4 2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [2-(4-morpholin -4-yl-phenyl)-ethyl]-amide 4 2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid {2-[4-(3-diethyl)] amino-pyrrolidin-1-yl)-phenyl ]-ethyl}-amide	۵		-
y-1H-benzoimidazole-4-carbo xylic acid [2-(4-amino- phenyl)-ethyl]-amide  4	4-aminophenet	2 8.20(m, 2H), 7.79(d, 1H), 7.49(d, 2H), 7.42(t, 2H),	7.49(d, 2H), 7.42(t, 2H),
xylic acid [2-(4-amino-phenyl)-ethyl]-amide  4	oo hylamine	7.32(d, 2H), 6.86(d, 1H), 3.74(t, 2H), 3.06(t, 2H)	4(t, 2H), 3.06(t, 2H)
phenyl)-ethyl]-amide  2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [2-(4-morpholin -4-yl-phenyl)-ethyl]-amide  2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid {2-[4-(3-diethyl amino-pyrrolidin-1-yl)-phenyl ]-ethyl}-amide			
4 2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [2-(4-morpholin -4-yl-phenyl)-ethyl]-amide 4 2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid {2-[4-(3-diethyl)] amino-pyrrolidin-1-yl)-phenyl ]-ethyl}-amide			,
y-1H-benzoimidazole-4-carbo xylic acid [2-(4-morpholin -4-yl-phenyl)-ethyl]-amide 4	x 2-(4-morpholi	2 8.14(m, 2H), 7.78(d, 1H), 7.41(d, 2H), 7.35(d, 1H),	.41(d, 2H), 7.35(d, 1H),
xylic acid [2-(4-morpholin -4-yl-phenyl)-ethyl]-amide  2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid {2-[4-(3-diethyl amino-pyrrolidin-1-yl)-phenyl ]-ethyl}-amide	o n-4-yl-phenyl)	7.14(d, 2H), 6.85(d, 1H), 3.89(m, 4H), 3.71(t, 2H),	89(m, 4H), 3.71(t, 2H),
4 2-(4-fluoro-phenyl)-ethyl]-amide y-1H-benzoimidazole-4-carbo xylic acid {2-[4-(3-diethyl amino-pyrrolidin-1-yl)-phenyl ]-ethyl}-amide	-ethylamine	3.28(m, 4H), 2.96(t, 2H)	
4 2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid {2-[4-(3-diethyl amino-pyrrolidin-1-yl)-phenyl ]-ethyl}-amide			
dazole-4-carbo I-(3-diethyl n-1-yl)-phenyl	x {1-[4-(2-amin	2 8 8.13 (m, 1H), 7.78 (d, 1H), 7.32~7.20 (m, 4H),	l), 7.32~7.20 (m, 4H),
!-(3-diethyl n-1-yl)-phenyl	o o-ethyl)-phen	7.11 (s, 1H), 6.74 (m, 2H), 6.48 (d, 1H), 3.60 (t,	6.48 (d, 1H), 3.60 (t,
n-1-yl)-phenyl	yl]-pyrrolidin-	2H), 2.90 (t, 2H), 2.82~2.71 (m, 6H), 2.40 (q,	.71 (m, 6H), 2.40 (q,
	rl 3-yl}-diethyl-	4H), 1.65 (m, 1H), 1.02 (t, 6H)	(H9
	amine		

4 2-(4-fluoro-phenyl)-7-hydrox N-[4-(2-amin 2 y-1H-benzoimidazole-4-carbo o-ethyl)-phen xylic acid {2-[4-(2-yl)-2-morpholi yl]-2-morpholi	-7-hydrox N-[4-(2-amin e-4-carbo o-ethyl)-phen yl]-2-morpholi			8 8.15(m, 2H), 7.79(d, 1H), 7.53(d, 2H), 7.39(t, 2H), 7.29(d, 2H), 6.87(d, 1H), 4.13(s, 2H), 3.97(br, 4H), 3.72(q, 2H), 3.44(br, 4H), 2.97(t, 2H)
		morpholin-4-yl-acetylamino)- phenyl]-ethyl}-amide	n-4-yl-acetam ide	
135	4	2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [2-(4-dimethyl amino-phenyl)-ethyl]-amide	N,N-(dimethyl 2 amino)pheneth ylamine	6 8.20(m, 3H), 7.78(d, 1H), 7.54(m, 3H), 7.43(t, 2H), 6.84(d, 1H), 3.75(t, 2H), 3.21(s, 6H), 3.07(t, 2H)
136	4	2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid {2-[4-(2-morpholin -4-yl-ethoxy)-phenyl]-ethyl} -amide	2-[4-(2-morp 2 holin-4-yl-eth oxy)-phenyl]- ethylamine	6 8.18(m, 2H), 7.79(d, 1H), 7.42(t, 2H), 7.26(d, 2H), 7.00~6.85(m, 3H), 4.33(m, 2H), 4.10~4.00(br, 2H), 3.95~3.75(br, 2H), 3.75~3.50(m, 8H), 3.32(m, 4H), 2.95(m, 2H)
137	4	2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [2-(2-hydroxy -phenyl)-ethyl]-amide	2-hydroxyphen 2 ethylamine	5 8.18(m, 2H), 7.78(d, 1H), 7.38(t, 2H), 7.14(d, 1H), 7.03(d, 1H), 6.88~6.74(m, 3H), 3.77(t, 2H), 2.98(t, 2H)

138	4	2-(4-fluoro-phenyl)-7-hydrox	2-methoxyphe	2	6 8.18~8.05(m. 2H), 7.78(d. 1H), 7.45~7.25(m. 3H)
		y-1H-benzoimidazole-4-carbo	nethylamine	<del></del> _	7.20(m, 2H), 6.95(d, 1H), 6.82(d, 1H), 3.78(s, 3H),
		xylic acid [2-(2-methoxy-			3.73(t, 2H), 2.99(t, 2H)
		phenyl)-ethyl]-amide			
139	4	2-(4-fluoro-phenyl)-7-hydrox	3-bromophene	2	6 8.12(m, 2H), 7.80(d, 1H), 7.49(s, 1H),
		y-1H-benzoimidazole-4-carbo	thylamine		7.38~7.18(m, 5H), 6.83(d, 1H), 3.76(t, 2H), 2.97(t,
		xylic acid [2-(3-bromo-			2H)
		phenyl)-ethyl]-amide			,
140	5	2-(2,4-difluoro-phenyl)-7-hyd N-[4-(2-amin	┼──	2	8 7.92-7.89 (1H, m), 7.74 (1H, m), 7.30-7.11 (6H,
		roxy-1H-benzoimidazole-4-ca	o-ethyl)-phen		m), 6.74 (1H, d), 3.67 (2H, bs), 2.89 (2H, bs), 2.82
		rboxylic acid [2-(4-methane	yl]-methanesul		(3H, s)
		sulfonylamino-phenyl)-ethyl]-	fonamide		
		amide			
141	ಬ	2-(2,4-difluoro-phenyl)-7-hyd N-[4-(2-amin	<del> </del>	2	6 7.99 (1H, m), 7.74 (1H, d), 7.50 (2H, d), 7.33-7.26
		roxy-1H-benzoimidazole-4-ca	o-ethyl)-phen		(2H, m), 7.23 (4H, m), 6.94 (2H, d), 6.81 (1H, d), 3.58
		rboxylic acid {2-[4-(toluene	yl]-p-toluenes		(2H, t), 2.82 (2H, t), 2.23 (3H, s)
		-4-sulfonylamino)-phenyl]-et	ulfonamide		
		hyl}amide			

142	r2	2-(2,4-difluoro-phenyl)-7-hyd	N-[4-(2-amin   2	8 8.06 (1H, d), 7.81 (1H, d), 7.51-7.15 (6H, m), 6.88
		roxy-1H-benzoimidazole-4-ca	o-ethyl)-phen	(1H, d), 3.67 (2H, t), 3.01 (2H, q), 2.92 (2H, t), 1.25
		rboxylic acid [2-(4-ethane	yl]-ethanesulf	(3H, m)
	_	sulfonylamino-phenyl)-ethyl]-	onamide	
		amide		
143	9	2-(2-chloro-4-fluoro-phenyl)	<i>N</i> -[4-(2-amin   2	6 7.94 (1H, m), 7.84 (1H, m), 7.62 (1H, m), 7.43 (2H,
		-7-hydroxy-1H-benzoimidazol	o-ethyl)-phen	m), 7.38-7.24 (3H, m), 6.95 (1H, d), 3.65 (2H, t),
		e-4-carboxylic acid	yl]-methanesul	2.99-2.83 (5H, m)
		[2-(4-methanesulfonylamino-p   fonamide	fonamide	,
		henyl)-ethyl]-amide		
144	9	2-(2-chloro-4-fluoro-phenyl)	N-[4-(2-amin 2	6 7.91 (1H, m), 7.81 (1H, d), 7.62-7.54 (3H, m), 7.42
		-7-hydroxy-1H-benzoimidazol	o-ethyl)-phen	(1H, m), 7.20-7.11 (4H, m), 7.05-6.93 (3H, m), 3.61
		e-4-carboxylic acid	yl]-p-toluenes	(2H, t), 2.86 (2H, t), 2.32 (3H, s)
		(2-[4-(toluene-4-sulfonylami	ulfonamide	
		no)-phenyl]-ethyl}amide		
145	9	2-(2-chloro-4-fluoro-phenyl)	N-[4-(2-amin 2	6 7.83 (2Н, т), 7.56 (1Н, т), 7.36 (1Н, т),
		-7-hydroxy-1H-benzoimidazol	o-ethyl)-phen	7.18-7.11 (4H, m), 7.38-7.24 (3H, m), 6.92 (1H, d),
		e-4-carboxylic acid	yl]-ethanesulf	3.60 (2H, t), 2.99 (4H, m), 1.23 (3H, s)
		[2-(4-ethanesulfonylamino-ph	onamide	
		enyl)-ethyl]-amide		

146	9	2-(2-chloro-4-fluoro-phenyl)	N-[4-(2-amin 2	6 8.00~7.91(m, 2H), 7.57(d, 1H), 7.48~7.34(m, 3H),
		-7-hydroxy-1H-benzoimidazol	o-ethyl)-phen	7.19(d, 2H), 6.92(d, 1H), 3.66(t, 2H), 2.9(t, 2H),
		e-4-carboxylic acid [2-(4-	yl]-acetamide	2.09(s, 3H)
		acetylamino-phenyl)-ethyl]-a		
		mide		
147	9_	2-(2-chloro-4-fluoro-phenyl)	2-morpholin-4 2	8 8.00~7.90(m, 2H), 7.60(d, 1H), 7.43(t, 1H), 6.95(d,
		-7-hydroxy-1H-benzoimidazol	-yl-ethylamine	1H), 4.20~3.60(m, 8H), 3.46(t, 2H), 3.34~3.10(br,
		e-4-carboxylic acid (2-		ZH)
		morpholin-4-yl-ethyl)-amide		,
148	9	2-(2-chloro-4-fluoro-phenyl)	2-(4-methyl-p 2	6 7.98(m, 2H), 7.59(d, 1H), 7.40(t, 1H), 6.93(d, 1H),
		-7-hydroxy-1H-benzoimidazol	iperazin-1-yl)	3.80~3.50(br, 10H), 3.21(t, 2H), 2.95(s, 3H), 2.06(t,
		e-4-carboxylic acid	-ethylamine	ZH)
		[2-(4-methyl-piperazin-1-yl)		
		-ethyl]-amide		
149	9	2-(2-chloro-4-fluoro-phenyl)	pentanoic acid 2	8 7.92~7.82(m, 2H), 7.57(d, 1H), 7.46~7.37(m, 3H),
		-7-hydroxy-1H-benzoimidazol   [4-(2-amino-e	[4-(2-amino-e	7.20(d, 2H), 6.92(d, 1H), 3.66(t, 2H), 2.91(t, 2H),
7		e-4-carboxylic acid	thyl)-phenyl]-	2.34(t, 2H), 1.66(m, 2H), 1.40(m, 2H), 0.95(t, 3H)
		[2-(4-pentanoylamino-phenyl)	amide	
		-ethyl]-amide		
				_

150	9	2-(2-chloro-4-fluoro-phenyl)	4-hydroxyphen	2	5 7.92~7.83(m, 2H), 7.62(d, 1H), 7.43(t, 1H), 7.07(d,
_		-7-hydroxy-1H-benzoimidazol	ethylamine		2H), 6.94(d, 1H), 6.69(d, 2H), 3.62(t, 2H), 2.85(t, 2H)
		e-4-carboxylic acid [2-(4-			
		hydroxy-phenyl)-ethyl]-amide		<del></del> -	
151	9	2-(2-chloro-4-fluoro-phenyl)	N-(5-nitro-pyr	2	δ 8.85(s, 1H), 8.12(br, 1H), 7.79~7.85(m, 3H),
		-7-hydroxy-1H-benzoimidazol	idin-2-yl)-eth		7.63(d, 1H), 7.42(t, 1H), 6.95(d, 1H), 6.62(br, 1H),
		e-4-carboxylic acid	ane-1,2-diami		3.90~3.60(m, 4H)
		[2-(5-nitro-pyridin-2-ylamino	ne		
		)-ethyl]-amide			
152	9	2-(2-chloro-4-fluoro-phenyl)	<i>N</i> -[6-(2-amin	2	8 8.05~7.85(m, 3H), 7.79(d, 1H), 7.61(d, 1H), 7.42(t,
		-7-hydroxy-1H-benzoimidazol	o-ethylamino)-		1H), 7.14(d, 1H), 6.94(d, 1H), $3.80 \sim 3.60 (m, 4H)$ ,
		e-4-carboxylic acid [2-(5-	pyridin-3-yl]-		2.92(t, 3H)
		methanesulfonylamino-pyridin	methanesulfon		
		-2-ylamino)-ethyl]-amide	amide		
153	9	2-(2-chloro-4-fluoro-phenyl)	N-[6-(2-amin 2	2	6 7.92(m, 1H), 7.89(d, 1H), 7.58(d, 2H), 7.45(m, 3H),
		-7-hydroxy-1H-benzoimidazol	o-ethylamino)-		7.29(m, 3H), 6.92(d, 1H), 6.78(d, 1H), 3.72(t, 2H),
		e-4-carboxylic acid (2-[5-	pyridin-3-yl]-		3.61(t, 2H), 2.37(s, 3H)
	-	(toluene-4-sulfonylamino)-pyr	p-toluenesulfo		
		idin-2-ylamino]-ethyl}-amide	namide		

154	9	2-(2-chloro-4-fluoro-phenyl)	histamine 2	8 8.79(s, 1H), 8.00~7.0 2H), 7.62(d, 1H),
		-7-hydroxy-1H-benzoimidazol		7.50~7.35(m, 2H), 6.93(d, 1H), 3.76(t, 2H), 3.76(t,
		e-4-carboxylic acid [2-(1H-		2H), 3.10(t, 2H)
		imidazol-4-yl)-ethyl]-amide		
155	9	2-(2-chloro-4-fluoro-phenyl) N-[6-(2-amin	<i>N</i> -[6-(2-amin 2	8 8.57(s, 1H), 8.10~7.95(m, 2H), 7.88(d, 1H),
		-7-hydroxy-1H-benzoimidazol o-ethylamino)-	o-ethylamino)-	7.74(d, 1H), 7.50~7.30(m, 2H), 6.95(d, 1H), 4.10(t,
		e-4-carboxylic acid	pyridin-3-yl]-	2H), 3.65(t, 2H), 2.13(s, 3H)
		[2-(5-acetylamino-pyridin-2-	acetamide	
		ylamino)-ethyl]-amide		
156	9	2-(2-chloro-4-fluoro-phenyl)	<i>N</i> -[4-(2-Amin 2	8 7.97~7.80(m, 2H), 7.61(d, 1H), 7.59(d, 2H), 7.40(t,
		-7-hydroxy-1H-benzoimidazol	o-ethyl)-phen	1H), 7.25(d, 2H), 6.92(d, 1H), 3.67(t, 2H), 3.34(s,
		e-4-carboxylic acid (2-{4-[2	yl]-2-(4-meth	ZH), 3.10~2.75(m, 13H)
		-(4-methyl-piperazin-1-yl)-a	yl-piperazin-1	
		cetylamino]-phenyl}-ethyl)-a	-yl)-acetamide	
		mide		

(2-chloro-4-fluoro-phenyl)	<i>N</i> -[4-(2-amin	2	8 7.97~7.83(m, 2H), 7.61(d, 1H), 7.50(d, 2H), 7.39(t,
roxy-1H-benzoimidazol	o-ethyl)-phen		1H), 7.25(d, 2H), 6.91(d, 1H), 3.67(t, 2H), 3.34(s,
urboxylic acid (2-{4-[2-	yl]-2-(4-ethyl		4H), 3.21(q, 2H), 3.05~2.75(m, 8H), 1.35(t, 3H)
ıyl-piperazin-1-yl)-acet	-piperazin-1-y		
no]-phenyl}-ethyl)-amid	1)-acetamide		
-chloro-4-fluoro-phenyl)	<i>N</i> -[4-(2-amin	2	8 7.99(m, 1H), 7.84~7.70(m, 2H), 7.52(d, 2H),
ydroxy-1H-benzoimidazol	o-ethyl)-phen		7.35~7.25(m, 3H), 6.77(d, 1H), 4.08(s, 2H), 3.73(s,
carboxylic acid (2-[4-(2	yl]-2-dimethyl		2H), 2.97(m, 8H)
ethylamino-acetylamino)-	amino-acetami		
yl]-ethyl}-amide	de		
-chloro-4-fluoro-phenyl)	<i>N</i> -[4-(2-amin	2	6 7.94~7.82(m, 2H), 7.60(d, 1H), 7.52(d, 2H), 7.40(t,
lydroxy-1H-benzoimidazol	o-ethyl)-phen		1H), 7.28(d, 2H), 6.89(d, 1H), 4.08(s, 2H), 3.68(t,
	yl]-2-diethyla		2H), 3.31(q, 4H), 2.94(t, 2H), 1.34(t, 6H)
4-(2-diethylamino-acetyla	mino-acetamid		
)-phenyl]-ethyl}-amide	е		
-chloro-4-fluoro-phenyl)	N-[4-(2-amin 2	2	(1H, d), 7.90 (1H, m), 7.72 (1H, d), 7.47 (2H, d), 7.39
ydroxy-1H-benzoimidazol	o-ethyl)-phen		(1H, m), 7.13-7.06 (4H, m), 6.95(2H, d), 6.75 (1H, d),
carboxylic acid	yl]-p-toluenes		3.63 (2H, t), 2.85 (2H, t), 2.23 (3H, s)
1-(toluene-4-sulfonylami	ulfonamide		
henyl]-ethyl}amide			
	2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid (2-{4-[2-(4-ethyl-piperazin-1-yl)-acetylamino]-phenyl}-ethyl)-amid e 2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid {2-[4-(2-dimethylamino-acetylamino)-phenyl]-ethyl}-amide 2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid {2-[4-(2-diethylamino-acetylamino)-phenyl]-ethyl}-amide 2-(3-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid {2-[4-(toluene-4-sulfonylamino)-phenyl]-ethyl}amide	nidazol o-ethyl)-phen  [4-[2- yl]-2-(4-ethyl) -acet -piperazin-1-y -amid l)-acetamide  [4-(2- yl]-2-(4-ethyl) -amid l)-acetamid  [4-(2- yl]-2-dimethyl  [4-(2- yl]-2-dimethyl  [4-(2-amin)  [4-(2-amin)	nidazol o-ethyl)-phen (4-[2- yl]-2-(4-ethyl)-acet -piperazin-1-y -amid l)-acetamide l)-acetamide l)-acetamide de de de de acid yl]-2-diethyla acid yl]-2-diethyla mino-acetamid idazol o-ethyl)-phen acid yl]-2-diethyla ecetyla mino-acetamid enyl) N-[4-(2-amin idazol o-ethyl)-phen acid yl]-2-diethyla acid yl]-2-diethyla mino-acetamid acetyla mino-acetamid acid yl]-2-diethyla mino-acetamid acid yl]-phen acid yl]-p-toluenes ylami ulfonamide

161	2	2-(3-chloro-4-fluoro-phenyl)	<i>N</i> -[4-(2-amin	2	8 8.19 (1H, d), 7.95 (1H, m), 7.74 (1H, d), 7.42 (1H,	
		-7-hydroxy-1H-benzoimidazol	o-ethyl)-phen		t), 7.24 (2H, d), 7.13 (2H, d), 6.75 (1H, d), 3.68 (2H,	
		e-4-carboxylic acid	yl]-methanesul		t), 2.91 (2H, t), 2.81 (3H, s)	
		[2-(4-methanesulfonylamino-p fonamide	fonamide			
		henyl)-ethyl]-amide				
162		7-hydroxy-2-phenyl-1H-benz	n-butylamine	3	6 7.95-7.70 (2H, m), 7.69 (1H, d), 7.60-7.42 (1H,	309
		oimidazole-4-carboxylic acid			m), 7.41-7.23 (2H, m), 3.42 (2H, t), 1.78-1.56 (2H,	
		butylamide			m), 1.55-1.34 (2H, t), 0.97 (3H, t)	
163		7-Hydroxy-2-phenyl-1H-ben	1,3-diaminopro	3	8 8.10 (1H, d), 7.90 (1H, d), 7.68 (1H, d), 7.67-7.53	310
		zoimidazole-4-carboxylic acid	pane	က	(3H, m), 6.81 (1H, d), 3.65 (2H, t), 3.22-3.00 (2H, t),	
		(3-amino-propyl)-amide			2.05 (2H, t)	
164		7-hydroxy-2-phenyl-1H-benz	1-(3-aminopro	က	8 8.04 (1H, d), 7.81 (1H, d), 7.75-7.66 (3H, m), 6.96	378
		oimidazole-4-carboxylic acid	pyl)-2-prolidin		(1H, d), 6.87 (1H, d), 3.53-3.41 (6H, m), 2.39 (2H, t),	
		[3-(2-oxo-prolidine-1-yl)-pr	one		2.03 (2H, t), 1.90 (2H, m)	
		opyl]-amide				
165	$\vdash$	7-hydroxy -2- phenyl-1H-	1-(3-aminopro	m	6 9.05 (1H, s), 8.17 (2H, d), 7.84 (1H, d), 7.75 (1H,	361
		benzoimidazole-4-carboxylic	pyl)imidazole		s), 7.72-7.62 (3H, m), 7.55 (1H, s), 6.88 (1H, d), 4.40	
		acid (3-imidazol-1-yl-propyl)		<del></del>	(2H, t), 3.57 (2H, t), 2.28 (2H, m)	
		-amide				

166		7-hydroxy-2- phenyl-1H-	4-(3-aminopro	3	6 8.20-8.11 (2H, m), 7.86 (2H, d), 7.84-7.69 (1H,	380
		benzoimidazole-4-carboxylic	pyl)morphorine		m), 7.63-7.59 (2H, m), 4.10 (2H, t), 4.06 (2H, t), 3.80	
		acid (3-morphorine-4-yl-		-	(2H, t), 3.65 (2H, t), 3.54 (2H, t), 3.15 (2H, t), 2.14	
		propyl)-amide			(2H, m)	
167		7-hydroxy-2-phenyl-1H-benz	3-(2-methyl-i	က	6 8.18-8.11 (2H, m), 7.84 (1H, d), 7.73-7.63 (4H,	
		oimidazole-4-carboxylic acid	midazol-1-yl)-		m), 7.40 (1H, d), 6.89 (1H, d), 4.28 (2H, t), 3.59 (2H,	
		[3-(2-methyl-imidazol-1-yl)-	propylamine		t), 2.63 (3H, s), 2.25 (2H, m)	
		propyl]-amide				
168	2	2-(4-chloro-phenyl)-7-hydro	n-butylamine	8	8 8.10 (2H, d), 7.88 (1H, d), 7.66 (2H, d), 6.92 (1H,	343
		xy-1H-benzoimidazole-4-carb			d), 3.42 (2H, t), 1.78-1.56 (2H, m), 1.55-1.34 (2H, t),	
	_	oxylic acid butylamide			0.97 (3H, t)	
169	2	2-(4-chloro-phenyl)-7-	1-(3-aminopro	8	6 8.21-8.11 (2H, m), 7.82 (1H, d), 7.63-7.53 (2H,	412
		hydroxy-1H-benzoimidazole-4	pyl)-2-pyrrolid	<del></del>	m), 6.86 (1H, m), 3.60-3.38 (6H, m), 2.38 (2H, t),	
		-carboxylic acid [3-(2-0xo-	one		2.03 (2H, t), 1.89 (2H, m)	
		prolidin-1-yl)-propyl]-amide				
170	2	2-(4-chloro-phenyl)-7-hydro	1-(3-aminopro	33	8 9.03 (1H, d), 8.18 (2H, t), 7.81 (1H, d), 7.74 (1H,	395
		xy-1H-benzoimidazole-4-carb	pyl)imidazole		d), 7.64-7.53 (3H, m), 6.84 (1H, d), 4.40 (2H, t), 3.60	
		oxylic acid (3-imidazole-1-yl			(2H, t), 2.29 (2H, m)	
		-propyl)-amide		{		

2-(4	2-(4-chloro-phenyl)-7-hydro	4-(3-aminopro	3	6 8.21-8.10 (2H, m), 7.85 (1H, d), 7.61-7.54 (2H,	414
xy-1H	xy-1H-benzoimidazole-4-carb	pyl)-morphorin		m), 6.80 (1H, d), 4.05 (2H, t), 3.81 (2H, t), 3.68-3.46	
oxylic	oxylic acid (3-morphorine-4-yl	Ð		(4H, m), 3.17 (2H, t), 2.11 (2H, m)	
-prop	-propyl)-amide				
2-(4	2-(4-chloro-phenyl)-7-hydro	3-(2-phenyl-i	3	8 8.13 (2H, d), 7.87 (1H, d), 7.70 (1H, d), 7.64-7.53	473
xy-1	xy-1H-benzoimidazole-4-carb	midazol-1-yl)-		(5H, m), 7.47-7.25 (3H, m), 6.80 (1H, d), 4.41 (2H, t),	
oxyl	oxylic acid [3-(2-pentyl-	propylamine		3.53 (1H, t), 2.27 (2H, m)	
imid	imidazol-1-yl)-propyl]-amide				
2-(4	2-(4-chloro-phenyl)-7-hydro	3-(4-methyl-i	3	6 8.85 (1H, d), 8.17 (2H, t), 7.87 (1H, m), 7.68-7.57	409
xy-1	xy-1H-benzoimidazole-4-carb	midazole-1-yl)		(2H, m), 7.40 (1H, d), 6.89 (1H, d), 4.32 (2H, t), 3.59	
oxyl	oxylic acid [3-(4-methyl-	-propylamine		(2H, m), 2.37-2.20 (5H, m)	-
mid	imidazol-1-yl)-propyl]-amide			•	<u> </u>
2-(4	2-(4-chloro-phenyl)-7-hydro	3-(4,5-dichlor	3	8 8.13 (2H, t), 7.85-7.78 (2H, m), 7.65-7.55 (2H, m),	474
Ky-]	xy-1H-benzoimidazole-4-carb	o-imidazoel-1		6.87 (1H, d), 4.18 (2H, t), 3.54 (2H, m), 2.18 (2H, m)	
oxyl	oxylic acid [3-(4,5-dichloro-	-yl)-propylami			
mid	imidazol-1-yl)-propyl]-amide	ne			
3-(4	2-(4-chloro-phenyl)-7-hydro	3-(2-methyl-i	က	8 8.21-8.09 (3H, m), 7.68 (1H, d), 7.60-7.55 (3H,	421
(y-1	xy-1H-benzoimidazole-4-carb	midazole-1-yl)	_	m), 7.36 (1H, d), 4.28 (2H, t), 3.63 (2H, m), 2.60 (3H,	•
xyli	oxylic acid [3-(2-methyl-	-propylamine	-	s), 2.28 (2H, m)	
mida	imidazol-1-yl)-propyl]-amide				

		19		
377	446	429	448	
6 8.10 (2H, d), 7.88 (1H, d), 7.66 (2H, d), 7.37-7.23 (4H, m), 6.92 (1H, d), 3.42 (2H, t), 1.78-1.56 (2H, m), 1.55-1.34 (2H, t), 0.97 (3H, t)	5 8.07-7.74 (3H, m), 7.73-7.49 (1H, m), 6.90 (1H, d), 3.60-3.38 (6H, m), 2.38 (2H, t), 2.03 (2H, t), 1.89 (2H, m)	5 9.02 (1H, s), 7.90-7.72 (4H, m), 7.64-7.46 (2H, m), 6.88 (1H, d), 4.37 (2H, t), 3.53 (2H, t), 2.26 (2H, m)	8 8.03-7.76 (3H, m), 7.75-7.45 (1H, m), 6.85 (1H, d), 4.05 (2H, t), 3.81 (2H, t), 3.68-3.46 (4H, m), 3.17 (2H, t), 2.11 (2H, m)	5 8.15 (d, 2H), 8.11 (s, 1H), 7.86 (s, 1H), 7.64~7.29 (m, 5H), 7.29~7.25 (m, 3H), 6.56 (d, 1H), 4.41 (t, 2H), 3.53 (t, 2H), 2.27 (q, 3H)
က	က	က	က	က
n-butylamine	1–(3–aminopro pyl)–2–pyrolidi one	1-(3-aminopro pyl)imidazole	4-(3-aminopro pyl)morphorine	3-(2-phenyl-i midazol-1-yl)- propylamine
2-(2,4-dichloro-phenyl)-7- hydroxy-1H-benzoimidazole-4 -carboxylic acid butylamide	2-(2,4-dichloro-phenyl)-7- hydroxy-1H-benzoimidazole-4 -carboxylic acid [3-(2-oxo- pyrolidin-1-yl)-propyl]-amide	2-(2,4-dichloro-phenyl)-7- hydroxy-1H-benzoimidazole-4 -carboxylic acid (3-imidazol -1-yl-propyl)-amide	2-(2,4-dichloro-phenyl)-7- hydroxy-1H-benzoimidazole-4 -carboxylic acid (3-morphorin- 4-yl-propyl)-amide	2-(2,4-dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-c arboxylic acid [3-(2-phenylimidazol-1-yl)-propyl]-amide
က	က	က	က	က
176	177	178	179	180

5 8.84 (s, 1H), 7.91~7.73 (m, 3H), 7.58 (m, 1H), 7.38 (s, 1H), 6.85 (d, 1H), 4.29 (t, 2H), 3.54 (t, 2H), 2.34~2.25 (m, 5H)	5 7.91~7.81 (m, 4H), 7.52 (s, 1H), 6.96 (d, 1H), 4.15 (t, 2H), 3.64 (t, 2H), 2.13 (q, 2H)	8 8.11~8.09 (m, 3H), 7.61 (m, 2H), 7.45 (s, 1H), 6.88 (d, 1H), 4.31 (t, 2H), 3.46 (t, 2H), 2.25 (q, 2H), 2.33 (s, 3H)	8 8.10~8.05 (m, 3H), 7.58 (m, 2H), 7.40 (s, 1H), 6.88 (d, 1H), 4.22 (t, 2H), 3.60 (t, 2H), 3.02 (m, 1H), 1.3 (s, 6H)
က	ო	က	m
3-(4-methyl-i midazol-1-yl)- propylamine	3-(4,5-dichlor o-imidazol-1- yl)-propylamin e	3-(2-methyl-i midazol-1-yl)- propylamine	3-(2-isopropyl -imidazol-1-yl )-propylamine
2-(2,4-dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-c arboxylic acid [3-(4-methyl-imidazol-1-yl)-propyl]-amide	2-(2,4-dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-carboxylic acid [3-(4,5-dichloro-imidazol-1-yl)-propyl ]-amide	2-(2,4-dichloro-phenyl)-7-hy droxy-1H-benzoimidazole-4-carboxylic acid [3-(2-methylimidazol-1-yl)-propyl]-amide	2-(2,4-dichloro-phenyl)-7- hydroxy-1H-benzoimidazole-4 -carboxylicacid [3-(2- isopropyl-imidazol-1-yl)-prop yl]-amide
က	က	ო	က
181	182	183	184

185	4	2-(4-fluoro-phenyl)-7-hydrox	1-(3-aminopro	3	8 8.89 (1H, s), 8.21 (2H, m), 7.83 (1H, d), 7.49 (1H,
		y-1H-benzoimidazole-4-carbo	pyl)imidazole		s), 7.38-7.24 (3H, m), 6.90 (1H, d), 4.31 (2H, t), 3.56
		xylic acid (3-imidazol-1-yl-		· ·	(2H, t), 2.38-2.33 (2H, m)
		propyl)-amide			
186	4	2-(4-fluoro-phenyl)-7-hydrox	3-(2-isopropyl	က	8 8.26-8.21 (2H, m), 7.84 (1H, d), 7.65 (1H, s),
		y-1H-benzoimidazole-4-carbo	-imidazol-1-yl		7.46-7.37 (3H, m), 6.88 (1H, d), 4.34 (2H, t), 3.62
		xylic acid [3-(2-isopropyl-	)-propylamine		(2H, t), 3.52-3.43 (1H, m), 2.27 (2H, m), 1.36 (6H, d)
		imidazol-1-yl)-propyl]-amide			
187	4	2-(4-fluoro-phenyl)-7-hydrox	3-(4-methyl-	က	6 8.89 (1H, s), 8.21 (2H, m), 7.83 (1H, d), 7.43 (3H,
		y-1H-benzoimidazole-4-carbo	imidazol-1-yl)		m), 6.90 (1H, d), 4.31 (2H, t), 3.56 (2H, t), 2.38-2.27
		xylic acid [3-(4-methyl-	-propylamine		(5H, m)
		imidazol-1-yl)-propyl]-amide			
188	4	2-(4-fluoro-phenyl)-7-hydrox	3-(2-methyl-	က	8 8.29 (2H, m), 7.78 (1H, d), 7.49 (1H, s), 7.35-7.24
		y-1H-benzoimidazole-4-carbo	imidazol-1-yl)		(3H, m), 6.70 (1H, d), 4.26 (2H, t), 3.64 (2H, t),
	_	xylic acid [3-(2-methyl-	-propylamine		2.95(3H, s), 2.28 (2H, m)
	_	imidazol-1-yl)-propyl]-amide			
189	4	2-(4-fluoro-phenyl)-7-hydrox	3-(2-ethyl-	က	8 8.27 (2H, m), 7.79 (1H, d), 7.51 (1H, s), 7.33-7.25 (3H, m),
		y-1H-benzoimidazole-4-carbo	imidazol-1-yl)		6.72 (1H, d), 4.27 (2H, t), 3.65 (2H, t), 2.90(2H, q), 2.28 (2H,
		xylic acid [3-(2-ethyl-	-propylamine		m), 1.25 (3H, t)
		imidazol-1-yl)-propyl]-amide			

<del>-</del>			
8 8.24-8.16 (2H, m), 8.04 (1H, d), 7.79 (1H, d), 7.45-7.33 (2H, m), 6.99-6.84 (1H, m), 4.18 (2H, t), 3.54 (2H, t), 2.18 (2H, m)	5 8.20 (1H, q), 8.18-7.97 (1H, m), 7.86 (1H, d), 7.64 (1H, s). 7.45 (1H, s), 7.39-7.24 (1H, m), 6.86 (1H, d), 4.33(2H, t), 3.60 (2H, t), 3.49 (1H, m), 2.26 (2H, t), 1.36 (3H, s), 1.34 (3H, s)	6 8.23 (1H, q), 7.13-7.97 (1H, m), 7.84 (1H, d), 7.74 (1H, s), 7.56 (1H, s), 7.31-7.24 (2H, m), 6.84 (1H, d), 4.40(2H, t), 3.56 (2H, t), 2.28 (2H, t)	6 8.22 (1H, q), 8.14-7.98 (1H, m), 7.84 (1H, d), 7.40-7.27 (3H, m), 6.85 (1H, d), 4.30 (2H, t), 3.57 (2H, t), 2.30 (5H, m)
က	က	က	က
3-(4,5-dichlor o-imidazol-1- yl)-propylamin e	3-(2-isopropyl -imidazol-1-yl )-propylamine	1-(3-aminopro pyl)imidazole	3-(4-methyl- imidazol-1-yl) -propylamine
2-(4-fluoro-phenyl)-7-hydrox y-1H-benzoimidazole-4-carbo xylic acid [3-(4,5-dichloro-imidazol-1-yl)-propyl]-amide	2-(2,4-difluoro-phenyl)-7-hyd 3-(2-isopropy roxy-1H-benzoimidazole-4imidazol-1-y carboxylic acid [3-(2-isopropyl )-propylamine -imidazol-1-yl)-propyl]- amide	2-(2,4-difluoro-phenyl)-7-hyd 1-(3-aminopro roxy-1H-benzoimidazole-4-ca pyl)imidazole rboxylic acid (3-imidazol -1-yl-propyl)-amide	2-(2,4-difluoro-phenyl)-7-hyd roxy-1H-benzoimidazole-4-ca rboxylic acid [3-(4-methyl- imidazol-1-yl)-propyl]-amide
4	വ	വ	ಬ
190	191	192	193

	T :		
5 8.19-8.03 (2H, m), 7.81 (2H, m), 7.39-7.29 (1H, m), 6.85 (1H, d), 4.17 (2H, t), 3.52 (2H, t), 2.16 (2H, t)	5 8.21 (1H, q), 8.06 (1H, m), 7.85(1H, d), 7.62 (1H,s). 7.39-7.27 (2H, m), 6.87 (1H, d), 4.30(2H, t), 3.58 (2H, t), 2.63 (3H, s), 2.25 (2H, t)	5 8.29-8.05 (2H, m), 7.86 (1H, d), 7.64 (1H,s). 7.43 (1H, s), 7.38-7.31 (1H, m), 6.95 (1H, d), 4.29 (2H, t), 3.57 (2H, t), 3.03 (2H, q), 2.25 (2H, t), 1.34 (3H, t)	8 8.19-8.03 (2H, m), 7.81 (2H, m), 7.39-7.29 (1H, m), 6.85 (1H, d), 4.17 (2H, t), 3.52 (2H, t), 2.16 (2H, t)
က	m	က	င
3-(4,5-dichlor o-imidazol-1- yl)-propylamin e	3-(2-methyl-imidazol-1-yl)	3-(2-ethyl-imidazol-1-yl) -propylamine	3-(4,5-dichlor o-imidazol-1 -yl)-propylami ne
2-(2,4-difluoro-phenyl)-7-hyd 3-(4,5-dichlor roxy-1H-benzoimidazole-4-ca o-imidazol-1-rboxylic acid [3-(4,5-dichloro-yl)-propyl]-amide e	77 77	2-(2,4-difluoro-phenyl)-7-hyd roxy-1H-benzoimidazole-4-ca rboxylic acid [3-(2-ethyl-imidazol-1-yl)-propyl]-amide	2-(2,4-difluoro-phenyl)-7-hyd roxy-1H-benzoimidazole-4-ca rboxylic acid [3-(4,5-dichloro-imidazol-1-y l)-propyl]-amide
S	വ	2	ಬ
194	195	196	197

		84	
5 9.05 (1H, s), 8.00-7.88 (2H, m), 7.74 (1H, s), 7.66-7.57 (2H, m), 7.46-7.41 (1H, m), 6.95 (1H, d), 4.38(2H, t), 3.52 (2H, t), 2.25 (2H, t)	6 8.88 (1H, s), 8.00-7.87 (2H, m), 7.60 (1H, m), 7.41 (2H, m). 6.94 (1H, d), 4.28 (2H, t), 3.54 (2H, t), 2.29 (3H, s), 2.22 (2H, t)	5 7.94 (1H, m), 7.85 (1H, m), 7.76 (1H, s), 7.48 (1H, d), 7.30 (1H, t), 6.76 (1H, d), 4.17 (2H, t), 3.56 (2H, t), 2.16 (2H, t)	6 7.83 (1H, m), 7.50(1H, m), 7.39 (1H, s), 7.23 (2H, m), 7.13(1H, s), 6.76 (1H, d), 4.20(2H, t), 3.57 (2H, t), 2.47 (3H, s), 2.03 (2H, t)
က	м	ന	က
1–(3–aminopro pyl) imidazole	3-(4-methyl- imidazol-1-yl) -propylamine	3-(4,5-dichlor o-imidazol -1-yl)-propyla mine	3-(2-methyl-  azol   imidazol-1-yl)  acid   -propylamine  yl)-
2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid (3- imidazol-1-yl-propyl)-amide	2-(2-chloro-4-fluoro-phenyl) 3-(4-methyl7-hydroxy-1H-benzoimidazol imidazol-1-yl) e-4-carboxylic acid -propylamine [3-(4-methyl-imidazol-1-yl)-propyl]-amide	2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid [3-(4,5 -dichloro-imidazol-1-yl)-prop yl]-amide	2-(2-chloro-4-fluoro-phenyl) -7-hydroxy-1H-benzoimidazol e-4-carboxylic acid [3-(2-methyl-imidazol-1-yl)- propyl]-amide
9	9	9	9
198	199	200	201

202	2	2-(3-chloro-4-fluoro-phenyl)	nenyl) 3-(4-methyl-	3 8	3 6 8.87 (1H, s), 8.37 (1H, d), 8.17 (1H, m), 7.83 (1H,
		-7-hydroxy-1H-benzoimidazol imidazol	imidazol	q	d), 7.59 (1H, t), 7.40(1H, s), 6.84 (1H, d), 4.33 (2H,
	· <del>-</del> ··	e-4-carboxylic acid	acid  -1-yl)-propyla		t), 3.60 (2H, t), 2.25 (5H, m)
		[3-(4-methyl-imidazol-1-yl)-	mine		
		propyl]-amide			
203	2	2-(3-chloro-4-fluoro-phenyl)	1-(3-aminopro	3 8	2-(3-chloro-4-fluoro-phenyl) 1-(3-aminopro 3 6 9.05 (1H, s), 8.37 (1H, d), 8.17 (1H, m), 7.83 (1H,
		-7-hydroxy-1H-benzoimidazol pyl) imidazole	pyl) imidazole	===	m), 7.75 (1H, s), 7.61-7.43 (2H, m), 6.82 (1H, d),
		e-4-carboxylic acid (3-		4	4.41 (2H, t), 3.60 (2H, t), 2.30 (2H, t)
		imidazol-1-yl-propyl)-amide			,

10

15

25

30

35

<u>Example 204</u>: Preparation of 7-hydroxy-2-[4-(2-morpholin-4-ylethylamino)-phenyl]-1H-benzoimidazole-4-carboxylic acid [3-(4,5-dichloroimidazol-1-yl)-propyl]-amide

5 (1) Preparation of 3-[(4-nitro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester

Anhydrous *p*-toluenesulfonic acid (6.30 g, 33.1 mmol) was added to 50 ml of benzene and the resulting mixture was refluxed while removing water using a dean-stock trap. Added thereto were 3-amino-4-methoxy benzoic acid methyl ester (3 g, 16.6 mmol) obtained in step 1 of Preparation Example 1 and 4-nitrobenzonitrile (2.94 g, 19.9 mol), followed by stirring at 160 °C for 8 hours. The resulting solution was cooled to room temperature, the reaction was stopped by adding NaHCO<sub>3</sub> thereto, extracted with ethyl acetate, the extract was dried over MgSO<sub>4</sub> and concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (2.83 g, 8.59 mmol) in a yield of 52%.

- <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.12-8.09 (m, 2H), 7.82 (d,1H), 7.70-7.69 (m, 1H), 6.98 (d, 1H), 4.91 (bs, 2H), 3.89(s, 6H)
  - (2) Preparation of 2-(4-nitro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester

3-[(4-nitro-benzimidoyl)-amino]-4-methoxy-benzoic acid methyl ester (1.63 g, 4.95 mmol) was dissolved in 50% methanol, and 5% NaOCl was added dropwise thereto at room temperature. After checking the reaction by TLC, Na<sub>2</sub>CO<sub>3</sub> (1.05 g, 9.38 mmol) was added dropwise thereto and refluxed for 40 min. The resulting solution was cooled to room temperature, extracted with ethyl acetate and the extract was concentrated under a reduced pressure. The resulting residue was purified by silica gel column chromatography to obtain the title compound (0.75 g, 2.28 mmol) in a yield of 46 %.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 10.90 (bs, 1H), 8.36-8.31 (m, 4H), 7.95 (d, 1H), 6.78 (d, 1H), 4.16 (s, 3H), 4.01 (s, 3H)

(3) Preparation of 2-(4-amino-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid

2-(4-nitro-phenyl)-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester (0.63 g, 1.92 mmol) obtained in step 2 was dissolved in 15 ml of EtOH, 0.1 g of 10% Pd/C was added thereto and stirred for 24 hours while hydrogen was supplied thereto from a balloon fulfilled with H<sub>2</sub> gas. The resulting solution was filtered and dried to obtain the title compound (0.57 g, 1.92 mmol) in a yield of 100%.

10

20

5

 $^{1}$ H NMR (CH<sub>3</sub>OH- $d_4$ ): δ 10.48 (bs, 1H), 7.93 (d, 2H), 7.82 (d, 1H), 6.77 (d, 2H), 6.71 (d, 1H), 4.11 (s,3H), 3.98 (s, 3H)

(4) Preparation of 2-[(2-morpholinoethyl)-4-amino-phenyl]-7-methoxy-1Hbenzoimidazole-4-carboxylic acid methyl ester

2-(4-amino-phenyl)-7-hydroxy-1H-benzoimidazole-4-carboxylic acid (160 mg, 0.54 mmol) obtained in step 3 was dissolved in DMF, cesium carbonate (0.53 g, 1.61 mmol) was added thereto and stirred for 5 min. Added thereto were 2-chloroethylmorpholine (0.12g, 0.64mmol) and potassium iodide (0.18g, 1.08mmol), followed by stirring for 24 hours. Then, the resulting solution was extracted with ethyl acetate, the extract was concentrated under a reduced pressure, and the residue was purified by silica gel chromatography to obtain the title compound (91 mg, 0.22 mmol) in a yield of 41 %.

 $^{1}$ H NMR (CH<sub>3</sub>OH- $d_4$ ): δ 7.97 (d, 1H), 7.57 (d, 2H), 6.77-6.73 (m, 3H), 4.54 (t, 2H), 4.11 (s, 3H), 3.99 (s, 3H), 3.57-3.55(m, 4H), 2.64 (t, 2H), 2.31-2.28 (m, 4H)

30

25

- (5) Preparation of 2-[(2-morpholinoethyl)-4-amino-phenyl]-7-methoxy-1H-benzoimidazole-4-carboxylic acid-[3-(4,5-dichloro-imidazol-1-yl)-propyl]-amide
- 2-[(2-morpholinoethyl)-4-amino-phenyl]-7-methoxy-1H-benzoimidazole-4-carboxylic acid methyl ester (22 mg, 0.05 mmol) was dissolved in THF/H<sub>2</sub>O, LiOHH<sub>2</sub>O (6.7mg, 0.16mmol) was added thereto and

stirred at room temperature. The resulting solution was filtered to remove residual LiOHH<sub>2</sub>O, and the solvent was removed. The residue was dried and dissolved in DMF. Added thereto were 4,5-dichloro-1-(3-aminopropyl)imidazole (12.5mg, 0.06mmol), EDCI (30.9mg, 0.16mmol), DMAP (65.6mg, 0.54mmol) and HOBt (21.8mg, 0.16mmol), followed by stirring at room temperature. The resulting solution was extracted with ethyl acetate and concentrated under a reduced pressure. The resulting residue was purified by silica gel chromatography to obtain the title compound (19 mg, 0.03 mmol) in a yield of 63 %.

10

5

<sup>1</sup>H NMR (CH<sub>3</sub>OH- $d_4$ ): δ 7.93 (d, 1H), 7.77- 7.75 (m, 3H), 7.52 (d, 2H), 6.92 (d, 1H), 4.17 (t, 2H), 4.06-4.02 (m, 5H), 3.58-3.56 (m, 4H), 3.50 (t, 2H), 2.66 (t, 2H), 2.31-2.29 (m, 4H), 2.16 (q, 2H)

15 (6) Preparation of 2-[(2-morpholinoethyl)-4-amino-phenyl]-7-hydroxy-1H-benzoimidazole-4-carboxylic acid-[3-(4,5-dichloro-imidazol-1-yl)-propyl]-amide

2-[(2-morpholinoethyl)-4-amino-phenyl]-7-methoxy-1H-

benzoimidazole-4-carboxylic acid-[3-(4,5-dichloro-imidazol-1-yl)-propyl]-amide (15 mg, 0.03 mmol) obtained in step 5 was dissolved in MC, BBr<sub>3</sub> (1.0M solution in MC, 0.3mL, 0.3mmol) was added thereto and stirred at room temperature for 48 hours. The reaction was stopped by adding water thereto and the resulting solution was extracted with MC/MeOH (7:1). The extract was concentrated under a reduced pressure and purified by silica gel chromatography to obtain the title compound (5.9 mg, 0.01 mmol) in a yield of 40 %.

<sup>1</sup>H NMR (CH<sub>3</sub>OH- $d_4$ ):  $\delta$  7.95 (d, 1H), 7.81- 7.79 (m, 4H), 7.55 (d, 30 1H), 6.94 (d, 1H), 4.15 (t, 2H), 3.94 (t, 2H), 3.59 (t, 2H), 3.58-3.56 (m, 4H), 2.64 (t, 2H), 2.32-2.30 (m, 4H), 2.18 (q, 2H)

Test Example 1: Assay for GSK-3β inhibiting activity

35 The GSK-3β inhibiting activity was determined in accordance with the method of Shultz et al. described in US Patent No. 6153618, with minor modifications by using phospho-CREB peptide as a substrate.

5

10

15

20

25

30

35

First, PCR (polymerase chain reaction) was carried out using human DNA as a template as well as primers which were designed to correspond to the 3'- and 5' ends of the polynucleotide coding human GSK-3\beta gene (Genbank Accession No.: L33801). The BamH1/XhoI fragment of the amplified PCR product thus obtained was inserted into the pGex vector between the BamH1 and XhoI sites, and the vector obtained was transformed into *E. coli* BL21(DE3). The transformed cells thus obtained was incubated in LB agar plates (1% Bacto-trypton, 0.5% yeast extract, 1% NaCl) containing ampicillin (100  $\mu$ l/ml) until the optical density at 600nm reached about 0.5. The cultured mixture was cooled to 18 °C and isopropyl β-Dthiogalacto-pyranoside (IPTG) was added thereto to a final concentration of 0.5 mM. After 16 hours, the resultant was centrifuged at 10,000 x g for 10 min, the collected cells were suspended in a buffer solution (30 mM Tris-HCl (pH 7.5), 100 mM NaCl, 5% glycerol, 2mM DTT) and the cells were disrupted using Sonic Dismembrator (Fisher, U.S.A.) in a ice bath. The resulting solution was centrifuged at 16,000 rpm for 30 minutes. The supernatant was connected to GST (Glutathione-S-transferase) column (Pharmacia Biotech, U.S.A.) equilibrated in the same buffer solution, purified by glutathione affinity chromatography (eluent: 5 mM glutathione), and then, digested with thrombin to cleave the connecting site between the GST moiety and GSK-3ß protein. The purified GSK-3β protein was diluted in a buffer solution (20 mM HEPES (pH 7.5), 5% glycerol, 2 mM DTT) to a final concentration of 50 mM NaCl and the resulting solution was subjected to mono S column chromatography (eluent: linear gradient from 0M to 1M NaCl buffer) using mono S column (Pharmacia Biotech, U.S.A.) equilibrated in the same buffer solution to obtain GSK-3ß protein.

100 nM GSK-3 $\beta$  protein, 12.5 mM each of the compounds prepared in Examples 1 to 204 dissolved in DMSO, an assay buffer (50 mM Tris-HCl, pH 7.5, 10mM MgCl<sub>2</sub>, 1mM EGTA, 1mM DTT), 100  $\mu$ M phospho-CREB peptide (NEB, USA), 100  $\mu$ M ATP, <sup>32</sup>P-ATP and 1  $\mu$  Ci were reacted at 30 °C for 1 hour. The reaction was stopped by adding  $5\mu$ l of 5% phosphoric acid to 25  $\mu$ l of the resulting solution. The resulting mixture was centrifuged at 15,000 rpm for 10 min, 20  $\mu$ l of the supernatant was added dropwise to Whatman p81 filter paper, and then, the resulting filter paper was washed with 0.5% phosphate buffer for 10 min. The filter paper was further washed 3 times and the enzymatic activity was determined by examining the extent of phospho-CREB peptide phosphorylation which is

represented by the unit of count per minute (CPM), measured with a  $\beta$ -counter (Packard, USA).

The GSK- $3\beta$  inhibiting activity was then calculated in accordance with the following equation:

$$CPM(sample) - CPM(blank)$$
Degree of Inhibition (%) = 100 x [ 1 - ----- ]
$$CPM(control) - CPM(blank)$$

wherein the blank represents a value obtained without the use of the enzyme and the compound of the present invention, and the control, in the absence of the compound of the present invention.

The IC<sub>50</sub> value of the inventive compound was determined from the degree of inhibition (%) and the result is shown in Table 3.

15

5

Table 3

Exam.	IC <sub>50</sub> (μ Μ)	Exam.	IC <sub>50</sub> (µ M)	Exam.	IC <sub>50</sub> (μ M)	Exam.	IC <sub>50</sub> (μ M)
1	>1	52	>1	103	>5	154	>1
2	>1	53	>1	104	>1	155	>1
3	>1	54	>1	105	0.05	156	0.28
4	>1	55	>1	106	0.015	157	0.49
5	0.3	56	0.7	107	0.05	158	0.23
6	>1	57	0.58	108	>1	159	0.68
7	>1	58	0.67	109	0.03	160	>1
8	. >1	59	0.16	110	0.28	161	0.09
9	0.18	60	0.35	111	>1	162	0.24
10	0.04	61	>1	112	0.04	163	>1
11	>5	62	>1	113	0.19	164	0.84
12	0.2	63	0.45	114	0.001	165	0.08
13	0.36	64	0.03	115	0.026	166	>1

	T	<del></del>		·,·			
14	>1	65	0.06	116	0.003	167	0.1
15	0.11	66	>1	117	0.03	168	> 1
16	0.7	67	0.16	118	>5	169	>1
17	0.24	68	0.017	119	>5	170	0.19
18	>1	69	>1	120	0.07	171	>1
19	>1	70	>1	121	0.03	172	0.8
20	4.1	71	>1	122	0.2	173	0.1
21	>5	72	0.12	123	0.05	174	0.04
22	>1	73	>1	124	0.07	175	0.28
23	0.68	74	>1	125	>1	176	0.45
24	>5	75	0.009	126	>1	177	0.2
25	>1	76	0.05	127	0.18	178	0.04
26	>1	77	0.033	128	0.15	179	>1
27	>1	78	>1	129	0.12	180	0.21
28	0.74	79	0.12	130	0.33	181	0.03
29	0.08	80	0.07	131	0.17	182	0.008
30	>1	81	>1	132	0.19	183	0.06
31	>1	82	>1	133	>1	184	0.15
32	0.5	83	>1	134	0.04	185	>1
33	>1	84	>1	135	>1	186	0.05
34	>1	85	>5	136	0.24	187	0.01
35	0.007	86	0.25	137	0.005	188	0.002
36	>1	87	0.23	138	>1	189	>1
37	>1	88	0.22	139	0.12	190	0.006
38	>1	89	0.32	140	> 1	191	0.09

5

	Υ						
39	>1	90	0.13	141	0.043	192	0.008
40	>1	91	>1	142	0.001	193	0.02
41	>1	92	0.08	143	0.002	194	0.004
42	>1	93	>1	144	0.006	195	0.03
43	>1	94	>5	145	0.002	196	0.02
44	>1	95	>1	146	0.07	197	0.003
45	0.02	96	0.022	147	0.21	198	0.02
46	>5	97	0.17	148	>1	199	0.01
47	>5	98	>1	149	0.14	200	0.002
48	>5	99	1	150	0.06	201	0.07
49	0.6	100	0.2	151	0.4	202	0.009
50	0.6	101	>1	152	0.24	203	0.003
51	0.87	102	0.23	153	0.05	204	>5

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

## This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

□ BLACK BORDERS
□ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
□ FADED TEXT OR DRAWING
□ BLURRED OR ILLEGIBLE TEXT OR DRAWING
□ SKEWED/SLANTED IMAGES
□ COLOR OR BLACK AND WHITE PHOTOGRAPHS
□ GRAY SCALE DOCUMENTS
□ LINES OR MARKS ON ORIGINAL DOCUMENT
□ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY

## IMAGES ARE BEST AVAILABLE COPY.

☐ OTHER:

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.